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ARCHIVES OF DISEASE IN CHILDHOOD

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COMA WITH GLYCOSURIA NOT DUE TO DIABETES MELLITUS

BY

G. B. FLEMING, B.A., M.D., AGNES HERRING, M.B., CH.B., and NOAH MORRIS, M.D., D.Sc.

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It is well known that glycosuria with hyperglycaemia does not necessarily indicate true diabetes mellitus. The association, however, of coma with glycosuria, even though acetonuria is only slight, almost inevitably leads to the diagnosis of diabetic coma.

The first two cases described in this paper were admitted in profound coma and had abundant sugar in the urine. They were at first looked on as examples of diabetic coma but subsequently it became evident in both that the symptoms were due to another cause.

Case 1. J. McG., a boy of eleven years was admitted to hospital on January 29, 1929. At the age of two weeks he was treated surgically for a depressed fracture of the left frontal region. Apart from measles in early childhood he had been healthy till six months before admission. At that time he began to have attacks of headache and giddiness followed by vomiting which occurred about once a week and lasted for a day. Two weeks before admission vomiting occurred every second morning and a week later the boy was noticed to be very drowsy. Vomiting ceased for two days and then recurred in association with constipation and severe headache. On the day before admission the headache became more severe and on the same evening the boy became comatose and was sent to hospital early next morning (1 a.m.) as a case of meningitis.

On admission the patient was found to be a well-nourished boy in a semi-comatose condition. Physical examination revealed no abnormality in the heart, lungs and abdomen. Kernig's sign was present but nuchal rigidity was only slight. Lumbar puncture was performed and 40 c.c. of clear cerebro-spinal fluid was withdrawn under greatly increased pressure: the cell count was 13 per c.mm. and the Pandy test negative. The urine was found to contain abundant sugar and a moderate amount of acetone and diacetic acid.

Treatment was carried out immediately on the assumption that the condition was one of diabetic coma. Twenty units of insulin and 20 gm. of glucose were given: the boy soon regained consciousness. Six hours later (9 a.m.) the blood-sugar was 75 mgm. per 100 c.c. and the urine contained but a trace of sugar. The child now was bright and intelligent. His weight was 27·68 kgm. Physical examination revealed no abnormality

except that the right pupil was larger than the left and ophthalmoscopic examination showed optic neuritis in both eyes with numerous haemorrhages. Vision appeared to be normal and no restriction in the field of vision of either eye could be detected. On closer inquiry into the history it was found that the attacks of headache had been accompanied by vertigo, diplopia and dimness of vision but that there was no apparent defect between the attacks. A skiagram of the skull showed slight separation of the sutures, a large pituitary fossa with erosion of the posterior clinoid process and areas of calcification above the sella.

Four days after admission (30.1.29) a blood-sugar curve after 29 gm. glucose (1 gm. per kgm. body weight) gave the following result:—

FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS	
106	211	209	191	122	MGM. PER 100 C.C.

Sugar was present in the urine obtained one hour after ingestion of glucose.

Three weeks later (23.2.29) the blood-sugar curve after 29 gm. glucose gave the following result:—

FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS	
109	204	216	106	67	MGM. PER 100 C.C.

There was no glycosuria.

On 4.3.29 the blood-sugar curve after 29 gm. glucose was

FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS	
136	313	331	211	109	MGM. PER 100 C.C.

Sugar was present in the half-hour, hour and two hour specimens of urine.

Throughout the boy's stay in hospital (26.1.29 to 7.3.29) specimens of his urine occasionally contained a trace of glucose and glucosazone crystals were recovered.

Four months later (July, 1929) the boy was seen again as an out-patient, when he was found to have put on 9 kgm. in weight and showed the Fröhlich type of obesity. On ophthalmoscopic examination the fundi appeared normal. The blood-sugar after 25 gm. glucose was as follows:—

FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS	
135	227	241	152	136	MGM. PER 100 C.C.

There was no glycosuria.

Two years later (October, 1931) his weight was 43·2 kgm., height 147·5 cm. The blood-sugar curve after 43 gm. glucose was

FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS	
87·7	182	256	204·3	156·2	MGM. PER 100 C.C.

There was sugar and acetone in the specimen of urine obtained one hour after glucose was given.

It is clear that this case is one of supra-pituitary tumour, probably an adamantinoma giving rise to the typical Fröhlich syndrome with a disturbance in carbohydrate metabolism. The symptoms at first pointed

to a diagnosis of diabetic coma and it was only after further examination and observation that this diagnosis was proved to be unjustified. There can be no doubt, however, that the coma was due to increase in intracranial pressure with stimulation of the centre in the medulla controlling the blood-sugar level or more probably of the anterior pituitary lobe, the hormones of which have contra-insular and ketogenic properties. The association of coma with glycosuria almost automatically led to the diagnosis of diabetic coma. The one feature which was absent from the picture was typical acidotic breathing; this would almost certainly have been present in true diabetic coma.

Case 2. J. W., a boy aged two years, was admitted to hospital on the night of October 13, 1934. The birth and development of the child had been normal. The first tooth was cut at seven months, walking began at nine months, and talking at eighteen months. Except for measles at one year, followed by more or less persistent blepharitis, there had been no other illnesses. There was no history of thirst, polyuria or diarrhoea. On the day before admission the child was well. On the morning of the day of admission he was listless and tired and off his food. In the afternoon he seemed better, but in the evening he was febrile and he vomited. He was put to bed but did not sleep. On being lifted for a moment he suddenly became drowsy and did not recognize his parents. This condition persisted and he was brought to hospital two hours after the onset.

On admission the patient was found to be a pale, puny-looking child; he was unconscious but could be roused with difficulty. He lay motionless with closed eyes, breathing regularly but not deeply and showing no sign of air-hunger. The rectal temperature was 101° F. The pupils were equal and reacted to light, and the eyeballs were of normal tension. Neither nuchal rigidity nor Kernig's sign was present and the plantar reflexes were flexor. There was no oedema. The circulatory and respiratory systems appeared to be normal. The urine was found to contain abundant sugar, a faint trace of acetone, but no albumin or other abnormal constituent. At this time the patient was thought to be in diabetic coma, and was treated accordingly. Unfortunately a blood-sugar estimation was not made that evening. Treatment was carried out immediately; he was given 10 per cent. glucose in normal saline by stomach tube and by rectum (120 c.c. in all) and 10 units of insulin hypodermically. The child came out of coma rapidly. He was given sips of water containing sugar throughout the remainder of the night.

Next morning the child was awake, pale and cross but not thirsty. The urine was sugar-free and contained no ketone bodies. The blood taken at 9 a.m. had the low sugar content of 39 mgm. per 100 c.c. As the boy had been given sugar throughout the night this could not be considered a fasting value. The child was put on ordinary diet without insulin. By the afternoon abundant ketone bodies had appeared in the urine. Ketonuria persisted for the next seven days and then ceased. Apart from the specimen of urine obtained on the evening of admission, there was no glycosuria at any time during the child's stay in hospital.

On the morning of the second day in hospital following a twelve-hours' fast a blood-sugar curve was carried out after the

administration of 9 gm. of glucose by the mouth. The results showed a remarkably low fasting blood-sugar and a curve which did not reach the 100 mgm. level.

FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS	
28·5	66·6	96·1	69·2	66·6	MGM. PER 100 C.C.

A lumbar puncture was carried out. The cerebro-spinal fluid came out under normal pressure, was clear and contained 3 cells per c.mm. Pandy's test was negative. Ophthalmoscopic examination did not reveal any abnormality.

The child continued well on ordinary diet, but always seemed to be hungry and was cross. Three weeks later (November 2) another blood-sugar curve was carried out, this time after the administration of four minims of adrenaline hypodermically. The response was abnormally high.

FASTING	¼ HOUR	½ HOUR	1 HOUR	2 HOURS	
125	172·4	215·1	263·1	148·1	MGM. PER 100 C.C.

On November 6 the fasting blood-sugar was 81·5 mgm. per 100 c.c. and on November 30, 81·9 mgm. per 100 c.c.

The Wassermann reaction was negative. A skiagram of the skull taken during his stay in hospital showed no abnormality but one taken six months later showed separation of the sutures and 'splaying' of the sella indicating increased pressure. At this time the urine was found to be free from sugar and acetone and the fasting blood-sugar was 76·2 mgm. per 100 c.c.

There can be little doubt that this is not a case of true diabetes mellitus. The course of the illness is comparable to the metabolic disturbance produced by diabetic puncture, where all available carbohydrate is mobilized and excreted, leaving the tissues in a state of carbohydrate starvation with consequent hypoglycaemia. Presumably in the present case some sudden intracranial disturbance occurred leading to coma and mobilization and excretion of carbohydrate with consequent hypoglycaemia. The appearance of ketonuria twenty-four hours after the onset of the illness can be accounted for by the lack of carbohydrate in the tissues. The later skiagrams yield confirmatory evidence that the metabolic disturbance is related to some intracranial lesion possibly situated in the pituitary region. Whether the pituitary gland itself is involved it is impossible to say. If, however, this is the case it is possible that the glycosuria was due to sudden excitation of the anterior lobe with consequent suprarenal stimulation and inhibition of the action of insulin.

Another child recently observed by us shows clearly the influence of grave cerebral disturbances on the carbohydrate metabolism although in this case glycosuria was absent.

Case 3. E. G., a girl aged one year and eleven months was admitted to hospital on July 10, 1935. The birth was normal and the child remained healthy till three days before admission when she was noticed to be constipated and irritable. At 3 p.m. on the day of admission she suddenly became unconscious with rigid limbs, staring eyes and frothing at the mouth. She is also reported to have vomited.

On admission to hospital two hours after the onset of the illness she was found to be a moderately well-nourished child, deeply cyanosed and unconscious. The right arm and leg were held rigid and showed occasional twitching. The pupils were dilated and fixed. The knee jerks were active but the abdominal and plantar reflexes could not be elicited. Chvostek's sign was absent. The heart, lungs and abdomen appeared to be healthy. The urine contained neither albumin nor sugar. Lumbar puncture was done shortly after admission. The fluid was under increased pressure; it was clear and contained 3 cells per c.mm. Pandy's test was negative. Temperature 103° F.

The next morning the child appeared quite well though rather irritable.

The blood-sugar content was estimated at hourly intervals from the time of admission (5 p.m.) till midnight and again at 9 a.m. on the following day. The first sample showed 250 mgm. sugar per 100 c.c. and there was a gradual fall till the sample obtained twenty-four hours later only contained 36·7 mgm. per 100 c.c. (see table).

TABLE.

CASE 3. SHOWING THE CHANGES IN BLOOD-SUGAR CONTENT.

	5 P.M.	6 P.M.	7 P.M.	8 P.M.	9 P.M.	11 P.M.	MIDNIGHT	9 A.M.	NOON	5 P.M.
MGM. PER 100 C.C.	250·0	204·1	125·0	71·2	56·2	52·3	52·0	42·6	55·5	36·7

The fasting blood-sugar forty hours after admission was normal (82·6 mgm. per 100 c.c.) but the blood-sugar curve after 9 gm. glucose showed rather a high rise and a delayed fall.

FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS	
82·6	188·6	153·8	126·5	101·0	MGM. PER 100 C.C.

Eight hours after admission acetone was detected in the urine. A skiagram of the skull showed a suggestion of ' paw-marking ' in the parietal and occipital regions. The sutures did not appear to be separated.

Whatever the cause of the coma, there is clearly present in this case a disturbance of carbohydrate metabolism as indicated by the initial hyperglycaemia followed by hypoglycaemia and acetonuria, though the level of the blood-sugar apparently did not attain a height sufficient to cause glycosuria.

Discussion

A case in many ways similar to the three we have reported is described by Eckstein[1].

In this case, a girl of twelve years, who had not previously been known to have diabetes, was admitted to hospital in profound coma, with 9·2 per cent. of sugar in the urine and ketonuria. The blood sugar was 576 mgm.

per cent. She was treated with insulin and injections of glucose. The next day the patient regained consciousness, the excretion of ketones and sugar ceased and although the blood-sugar became normal, convulsions with an extensor plantar reflex occurred after a few hours. During the next few days severe nervous symptoms developed and persisted till she died ten weeks later. At autopsy marked atrophy of the cerebral cortex was found and on histological examination necrosis of the cerebral cortex and hippocampus.

This case was looked on as primarily one of diabetes with secondary involvement of the central nervous system but the fact that sugar disappeared from the urine and that the blood-sugar content returned to normal a considerable time before the girl died suggests that the glycosuria and coma were secondary to disease of the central nervous system. Though the blood-sugar was not estimated at the time, the convulsions and extensor plantar reflex which occurred the day after admission to hospital, suggest a swing over to a condition of hypoglycaemia as occurred in two of the cases here reported. In short it seems probable that the coma and glycosuria were not due to true diabetes mellitus.

The sequence of events in these cases in many ways resembles that reported by Greenwald and Eliasberg[2] in experimental burns in rabbits. These authors describe two stages, (1) an initial period of hyperglycaemia due to hyperactivity of the suprarenals and (2) a period of hypoglycaemia due to suprarenal exhaustion. They also record the case of two children with extensive burns in whom there was extreme hypoglycaemia and marked acetonuria.

Conclusions.

Three cases are reported in which sudden coma was associated with disturbance in carbohydrate metabolism. In none of them was the coma due to diabetes mellitus. In the first case there can be little doubt that the syndrome was caused by a lesion of the pituitary gland and in the second, though the evidence is not so strong, it is also possible that the pituitary gland was involved. The third case has not been under observation for sufficiently long a time to determine the cause of the syndrome but it is almost certainly of nervous origin.

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1. Eckstein, A., *Acta paediat.*, Uppsala, 1933, XVI, 601.
2. Greenwald, H. M., & Eliasberg, H., *Am. J. Med. Sci.*, Philad., 1926, CLXXI, 682.

A STUDY OF THE SEDIMENTATION RATE IN JUVENILE RHEUMATISM

BY

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(From the Hospital for Sick Children, Great Ormond Street and the I.C.A.A. Children's Heart Hospital, West Wickham.)

In a previous communication[3] a simple method of estimating the sedimentation rate (S.R.) was described which had the great advantage of requiring only a finger prick. Close agreement between the degree of rheumatic activity and the height of the sedimentation rate was demonstrated. This has been confirmed by Bach and Gray Hill[1], Struthers and Bacal[6], Perry[4] and others. In this paper it is proposed to record experiences in a larger series of cases, mostly patients at the Children's Heart Hospital, West Wickham, and coming under observation for varying periods from a few months to three years. The behaviour of the sedimentation rate in this larger series confirms the conclusions of the original investigation. Certain exceptions, however, were encountered which are not easy to explain and might well give rise to occasional difficulty in the interpretation of the test. Reference to these forms an important part of the present communication.

The sedimentation rate in relation to the rheumatic state.

The patients were divided into active and non-active cases, a clinical grouping which was made without reference to the result of the sedimentation rate. The criteria of activity have been pulse rate, temperature, weight and cardiac signs. In doubtful cases the electro-cardiograph was occasionally employed. From the outset it was recognized that other conditions can produce an increased sedimentation rate and allowance has been made for a transient rise due to intercurrent infections such as common colds, influenza, tonsillitis and otitis media. The normal sedimentation rate is between 3–10 mm., but here it has not been considered abnormal unless it exceeded 14 mm. The following is a brief summary of the results obtained in two hundred and twenty-nine children. The number of observations on each patient averaged seven; occasionally the test was only performed once, but in some it was repeated as often as twenty times.

Non-active cases. There were one hundred and forty children with no evidence of active rheumatism during the period of observation. Seventy-four of these had no signs of cardiac involvement and, with three exceptions, showed no rise in the sedimentation rate apart from intercurrent infections. There was no apparent reason for the raised values (17, 21 and 29 mm. maximum) in the three cases, except for tonsillar sepsis in one instance.

* Working with a grant from the Harmsworth Research Fund.

Sixty-six children had had heart disease at some time or other. The sedimentation rate was normal in fifty-six and raised in ten. In five this rise was transitory.

Active cases. Active rheumatism was present in eighty-nine cases. Sixty-six showed rapid improvement and were finally considered no longer active from the clinical standpoint. The sedimentation rate showed a corresponding fall to normal in fifty-eight. In seven the sedimentation rate was higher or lower than was to be expected, and in one apparently quiescent case a fresh rise in the sedimentation rate appeared to herald a re-awakened activity with chorea sometime after returning home.

In sixteen cases the activity was marked and prolonged. Here without exception the sedimentation rate was raised in close agreement with the clinical condition (cf. Payne[3]).

Seven fatal cases occurred. All but one showed a raised sedimentation rate, but curiously enough not so high as in many of the acute cases which recovered. In the one case with normal values cardiac failure was prominent (see p. 409). Hence with every type of rheumatism there is close agreement between the S.R. and the clinical picture and this has been confirmed in many cases in this series by the subsequent history. In fact, in only twenty out of the whole two hundred and twenty-nine cases was there any discrepancy.*

From these results, therefore, it appears justified to regard the S.R. as a valuable test which allows observation of the progress of rheumatic children to be made with great accuracy. Those who make use of it, however, must not forget that many other conditions besides active rheumatism may increase the sedimentation rate. Any acute fever or inflammatory lesion may do this, but it has been repeatedly noticed in the course of the present investigations that the common cold without complications appears not to affect it.

The influence of other disorders on the sedimentation rate.

Acute tonsillitis or naso-pharyngitis generally produces a rise in the S.R. (20–40 mm.) lasting two or three weeks, after which as a rule it drops to normal. A relapse or some other complication such as otitis or adenitis will delay this. Acute throat infections associated with influenza, on the other hand, behave differently, and the S.R. even in the absence of complications often takes a long time to settle. This is of distinct clinical interest and reflects the latent severity of this infection.

The picture is complicated when either of these acute infections occurs in a rheumatic subject, and the duration of the raised S.R. will largely depend on the previous rheumatic state. Patients with non-active rheumatism will react like normal individuals to acute tonsillitis, the S.R. remaining raised for about two weeks only. A more prolonged disturbance of the S.R. (3–4 weeks) must be expected after tonsillitis in actively rheumatic patients and when a fresh wave of acute rheumatism follows, high S.R. figures continue for months. These points are illustrated

* In nine this could be almost discounted on the grounds that the reading was above normal on one occasion only.

in table 1, and when studying this it should be borne in mind that a relapse of rheumatism is more likely to follow tonsillitis than influenza.

TABLE 1.

Cases.	Duration in weeks.				Total number of cases.
	0-2	3-5	6-8	over 8	
Non-active rheumatism					
Influenza	5	8	1	1	15
Tonsillitis	7	3	0	0	10
Active rheumatism					
Influenza	0	5	0	1	6
Tonsillitis	0	5	6	4	15

To show the duration of increased S.R. in weeks following attacks of influenza or tonsillitis in rheumatic children.

Chronic tonsillar sepsis.—The importance of this has been fully recognized and an endeavour was made to see if the S.R. was affected. Mr. James Crooks, F.R.C.S., has kindly allowed reference to a series of children under his supervision who were suffering from definite tonsillar sepsis requiring operation. Among thirty-eight non-rheumatic cases, fourteen had values above 14 mm. at one time or another before operation, but only in seven was this a constant feature on the two or three occasions when the test was repeated. Thus it will be seen that with occasional striking exceptions chronic tonsillar sepsis on the whole does not affect the S.R.

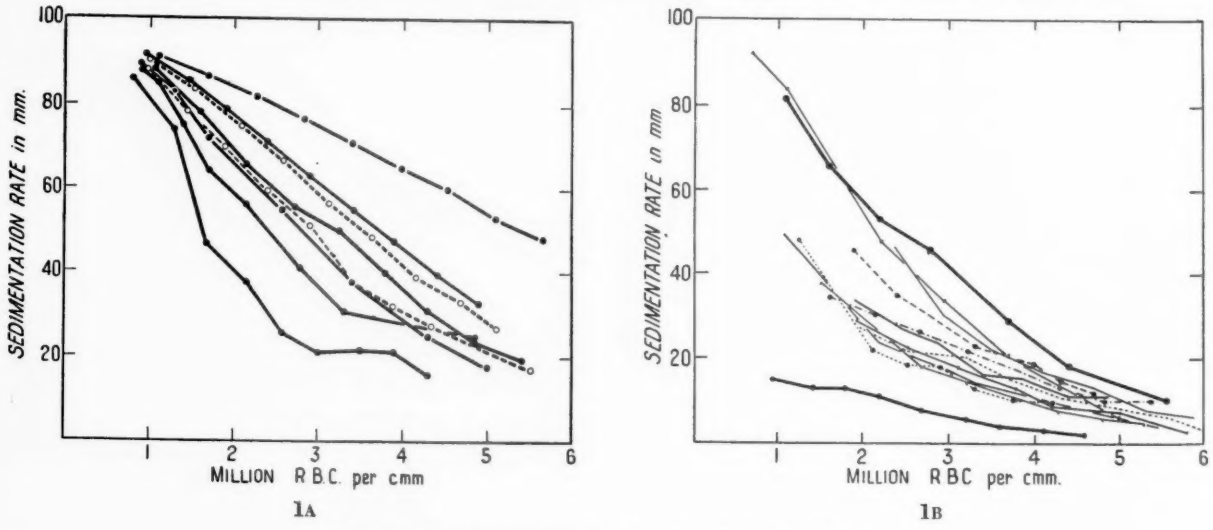
Tuberculosis.—A raised S.R. and failure to gain weight may also be the only obvious indication of this infection. In one young boy of six years, wrongly suspected of rheumatic carditis, the reason for a persistent high S.R. remained puzzling until a positive Mantoux test and radiographic evidence of large glands at the hilum revealed the true cause.

Rheumatoid arthritis.—When large numbers of rheumatic children are under supervision the rare inclusion of a case of rheumatoid arthritis in its earliest stages is apt to be misleading. A patient with this malady caused confusion for some time and an early active rheumatic carditis was expected in view of the history of fleeting joint pains, tachycardia, stationary weight and a considerable rise in the S.R. It was only later with the onset of the

characteristic thickening of the joint capsules and limitation of movement that the nature of the illness became clear.

Effect of anaemia.—It is generally recognized that anaemia has an effect on the S.R. Walton[7] has therefore suggested that the ideal method of performing the test would be first to bring the blood to a normal red count by removing a calculated amount of plasma from the centrifugalized blood, to suspend the red blood cells again in the remaining plasma and then to determine the S.R. This process is too cumbersome for routine use in a large number of cases and also has the additional disadvantage of requiring venu-puncture. While experimenting with this method, Walton also found that when specimens of blood obtained from different cases were diluted with their corresponding blood plasma until a red cell count of 1,000,000 per c.mm. had been reached, approximately the same S.R. reading (27·5 mm.*) was obtained, irrespective of what it had been originally. In other words, under the experimental condition of extreme dilution of the red blood cells relatively little difference was to be found between normal and pathological cases. Using 27·5 mm. as a constant standard figure for a red cell count of 1,000,000, Walton constructed a graph showing the variations in the S.R. in relation to the different dilutions of the red blood cells. The curve obtained almost described a straight line and it was claimed that from this a corrected S.R. figure could be estimated in any case, taking into account the degree of anaemia present.

An attempt was made to apply these observations to the method employed in testing the S.R. The experiments are illustrated in fig. 1 A and B



1A 1B

FIG. 1.—To show the effect on the S.R. of diluting blood with its own plasma. 'Artificial anaemia.' The R.B.C. count indicates the degree of dilution.

A. 8 subjects with high sedimentation rates.
B. 12 subjects with normal sedimentation rates.

* Owing to the difference in technique this corresponds to a value of about 85-90 mm. in our method.

and do not confirm Walton's findings. The value of the S.R. with the red cells diluted to 1,000,000 per c.mm. was by no means constant, varying in patients with active rheumatism between 81 and 92 mm. and in a group of healthy, normal controls, between 15 and 86 mm. Furthermore, although in some cases the plotted readings of the S.R. in relation to different red cell counts were found to describe a straight line on a graph, this was not the rule. The S.R. readings gave the most divergent results in the region of 3 to 5 million, where the red blood cell count would naturally fall in the majority of cases.

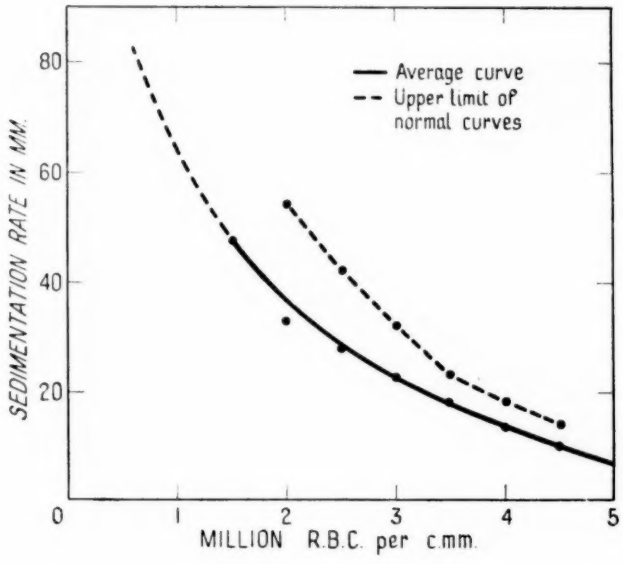


FIG. 2.—To show the average and maximal values of the S.R. in normal subjects at various R.B.C. counts.

Wintrobe and Lansberg[9] have obtained similar curves to those here described. They constructed an average curve from them and a chart which enabled the correction for the cell count to be read for any given sedimentation reading. A S.R. value calculated in this manner showed wide variation in many cases from that obtained by direct reading, after the blood had been artificially adjusted to a normal cell count.

In the absence of any accurate method of making corrections for anaemia a graph has been constructed, fig. 2, showing the average normal value of the S.R. at any known red cell count. The S.R. reading obtained in a given case is compared with the figure on the graph at the corresponding

red cell count. If the former is higher it may be assumed that the S.R. is increased apart from any effect due to anaemia.

Chorea.—In the course of this work it has been found that the S.R. is not affected in the same manner by chorea as it is by other forms of active rheumatism. Fifty cases were investigated in which chorea was the salient feature, although in some instances it was associated with other manifestations of acute rheumatism. With only a few exceptions the patients were kept under observations for at least six months after the chorea had subsided. It soon became apparent that the close parallelism between the height of the S.R. and the degree of active disease present, which has already been noted in various forms of acute rheumatism, does not hold good in regard to chorea. In twenty-eight of these fifty cases the S.R. remained raised for a short time only after admission to hospital, and in twenty-two it was never above normal. Many of the S.R. figures obtained were in fact, abnormally low, readings of 3, 2 or even 1 mm. being relatively common. This appeared to be such a striking feature in children subject to chorea that it was questioned whether or not S.R. values of 10–14 mm., generally regarded as normal, should be considered in chorea a sign of active disease. Seven patients developed chorea whilst under observation. In three the onset of the condition caused no increase in the S.R. and in the other four the rise was only transitory, the figures obtained being 15, 15, 18, and 45 mm. respectively.

Perry[4], Warner[8], and Struthers and Bacal[6] have all commented on the slight effect of acute chorea on the sedimentation rate. In their reports even less deviation from the normal was discovered than in the present series of cases. On the whole the present results lead to the belief that chorea generally produces a slight alteration in the S.R. It was hoped that the test would enable cases of chorea to be picked out which would be likely to develop cardiac disease, a high S.R. giving an indication that this might happen and vice versa. The same group of fifty cases was therefore studied in regard to this. The results were as follows and demonstrate that no reliance can be placed on the S.R. in this respect:—

S.R. during chorea.	Evidence of fresh cardiac disease.	
	Absent.	Present.
Normal	16	6
Between 14–20 mm.	7	3
Over 20 mm.	11	7

In conducting these investigations it was difficult to exclude with certainty one possible fallacy. Unless a patient is under almost continuous observation, detection of heart disease for the first time six to twelve months after an attack of chorea does not necessarily mean that the one is the direct outcome of the other. As is emphasized elsewhere in this paper mild attacks of rheumatic fever may pass unnoticed. Such an attack during the intervening twelve months, and not the chorea as observed, might easily have been the true origin of the fresh cardiac involvement. Two of the

six cases which developed carditis were under such constant supervision that the heart disease could definitely be attributed to the chorea. In these two cases the S.R. tested at the time of the chorea and repeatedly examined during the subsequent months never rose above normal.

Congestive failure.—Cardiac failure has a curious effect on the S.R. However active the rheumatic process may be, the onset of congestive failure and oedema causes the S.R. to fall from its previous high figure. The fall may continue to a level which in any other circumstances would be considered normal. Hässler and Möller[2], Struthers[6], and Perry[4] have all recorded such cases, and the phenomenon has been observed by us in at least eight patients (fig. 3). The fall of the S.R. may occur before any definite signs of failure are noticed, and at the time of the observation in one case there was even an apparent clinical improvement. Undoubtedly the fall often precedes the appearance of oedema, and it is believed that it occurs approximately at the time of hepatic enlargement. The converse of the same phenomenon was also observed. In three cases of severe active rheumatism the S.R. had fallen in the manner described with the onset of congestive failure. The clinical condition gradually improved under treatment, the oedema subsided and the S.R. rose above normal again. One patient ultimately recovered and the S.R. slowly returned to normal, proving this time that the rheumatic process had ceased to be active. Such a case is the exception and as all the remaining patients in this group died, a fall of the S.R. without clinical improvement or subsidence of rheumatic activity must be regarded as a bad prognostic sign. The cause of these effects is not known, but since it is generally assumed that the most important single factor influencing the S.R. lies in the composition of the plasma proteins, in particular the fibrin, analysis of the blood plasma was made in two cases. The results obtained were as follows:—

Plasma proteins.	Case D.	Case S.	Normal.
Albumin	3·25 per cent.	3·00 per cent.	4·4 per cent.
Globulin	1·99 ,, ,,	2·44 ,, ,,	2·1 ,, ,,
Fibrin	0·30 ,, ,,	0·43 ,, ,,	0·3 ,, ,,
Blood count, r.b.c.	4,309,000 per c.mm.	3,710,000 per c.mm.	
Sedimentation rate	5	21	
Corrected S.R. for 5,000,000 r.b.c. ...	4	6	

Judging from the experience of others (Rourke and Ernstene[3]) in acute rheumatism, and from our unpublished observations in active rheumatoid arthritis with a raised S.R., the plasma fibrin content and the albumin-globulin ratio in case D are much nearer the normal than is usually found. Had these chemical changes in the blood also been present in case S in association with cardiac failure, they might have accounted for the spurious fall of the S.R. but in case S the values obtained are such as would lead one to expect a high S.R. It appears from these two isolated investigations that the explanation may have to be sought elsewhere.

Discussion.

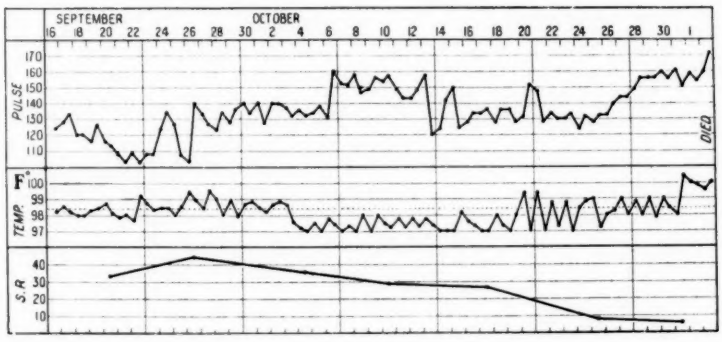
Those who make use of the test in regard to rheumatism must understand that it is in no way specific. Nearly all pyrexial infections are followed by a high sedimentation rate and inflammatory lesions unaccompanied by a rise in temperature may also behave in the same way. It is a most useful and sensitive method of estimating the degree of active rheumatism present, but it would be misleading to place complete reliance on it to the exclusion of all other criteria. Due regard must also be paid to the patient's general condition, the sleeping pulse rate, the physical signs present and the temperature and weight charts. A single high reading should not be trusted, but a constant high S.R. suggests an active rheumatic state.

Obvious rheumatic fever or active carditis, the latter often apyrexial, is pre-eminently characterized by a raised S.R. In the acute phase the test is almost superfluous, but later during convalescence it serves as a useful guide as to when the patient can be allowed to get up.

Miniature rheumatic fever.—The test has the greatest value following tonsillitis, since it is in this connection with such acute infections that rheumatic relapses are most often expected. Every degree of relapse has been observed, varying from an acute and virulent pericarditis with early death to the mildest forms of rheumatic fever. The latter has been termed by the authors ' miniature rheumatic fever.' It is characterized by slight degrees of fever, transient tachycardia and a persistent or fresh rise in the S.R. following the subsidence of the throat infection. The slightest cases produce no changes in the temperature or pulse rate and only affect the S.R. Otherwise they would pass unnoticed. They are of some interest in showing the latent tendency to relapse after tonsillitis although fortunately in most instances the patient's defences are able to overcome this (see fig. 4).

Sub-acute rheumatism.—The S.R. is a considerable help in indicating the line of treatment in sub-acute rheumatism, particularly as some authorities have begun to question the importance of ' growing pains ' in all instances. The present investigation indicates that a normal S.R. in such cases justifies the belief that the heart is in no danger and therefore allows less rigorous therapeutic measures. In old rheumatic cases a temporary rise in the S.R. has been repeatedly observed with the return of subacute pains in the limbs. Generally the temperature is hardly affected, if at all, and the whole affair is over in a few days. There may already be heart disease present in these sub-acute rheumatic cases, dating from a previous acute attack, and the question then arises whether there is any fresh cardiac involvement. In the absence of any clinical signs of this, the S.R. furnishes the best answer, and if it is normal there is no indication for drastic precautions.

Chorea, and its influence on the S.R., has already been discussed in some detail. It is curious that the S.R. may be little affected in the most acute cases, whereas it may be appreciably raised in mild degrees of chorea. There is no means of foretelling what to expect. Certainly a normal S.R. in chorea does not preclude heart disease developing soon afterwards.



D. M., age 3 yr. Cardiac disease.

FIG. 3. (Case D.).–To show the fall of the S.R. with onset of congestive cardiac failure.

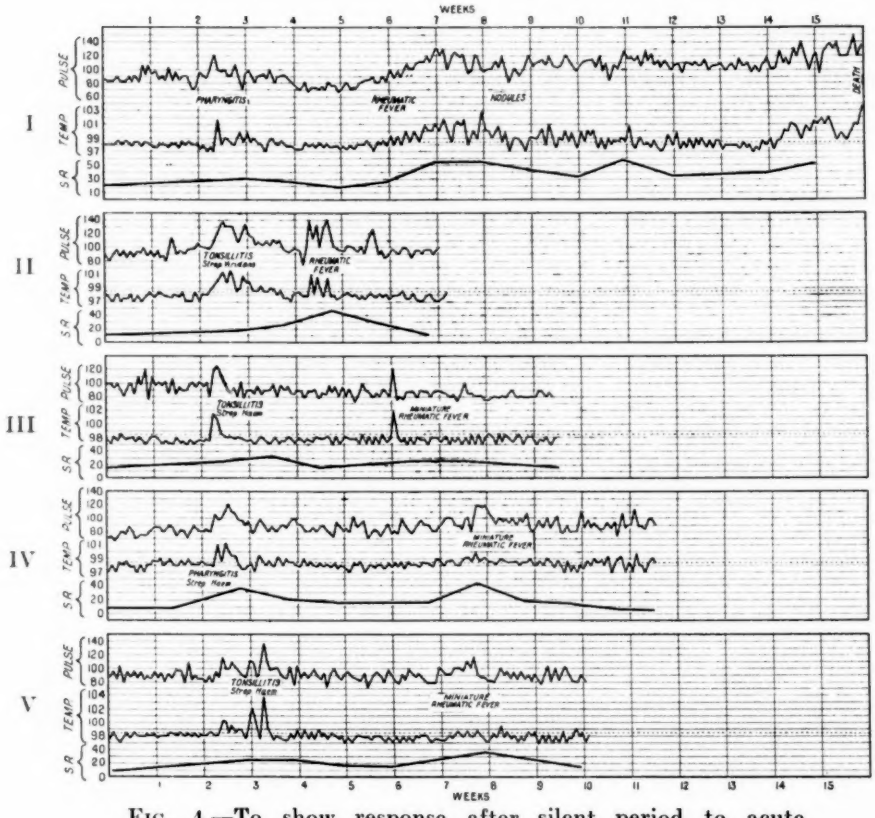


FIG. 4.—To show response after silent period to acute naso-pharyngeal infection in varying degree of severity.

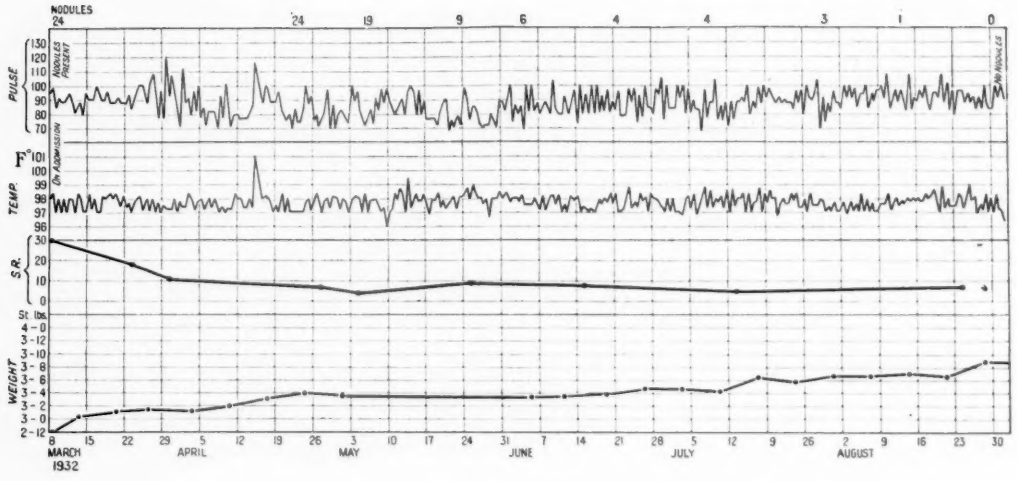
I. Rheumatic fever, pericarditis, nodules with fatal result.

II. Rheumatic fever. Rise in pulse, temperature, S.R.

III. 'Miniature rheumatic fever.' Transient rise in temperature and pulse. Rise in S.R. of longer duration.

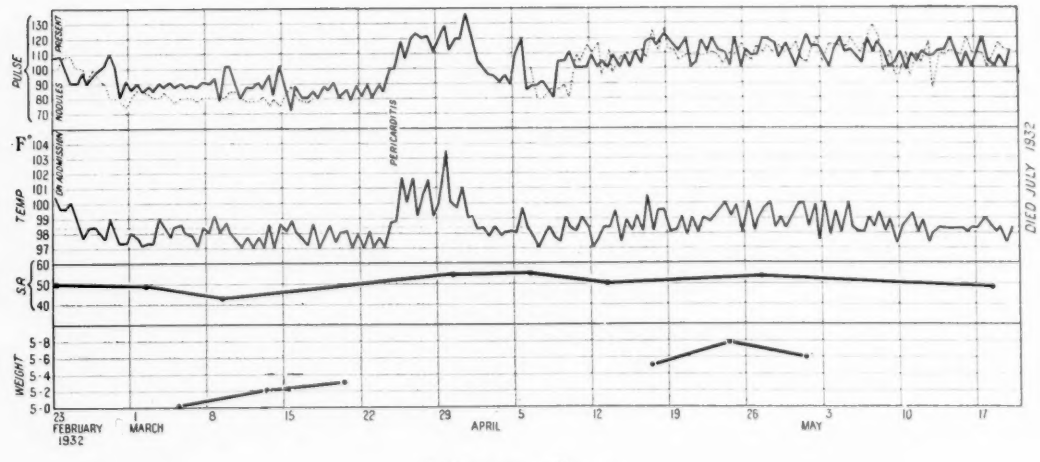
IV. 'Miniature rheumatic fever.' Rise in pulse rate, negligible rise of temperature. Definite rise of S.R.

V. 'Miniature rheumatic fever.' Slight rise in pulse rate, no rise of temperature. Definite rise of S.R.



P. P., age $8\frac{1}{2}$ yr.

FIG. 5.—To show falling S.R. in presence of nodules, active phase over, nodules disappear later.



I. E., age $12\frac{1}{2}$ yr.

FIG. 6.—Persistent raised S.R. in presence of nodules, active disease still present: terminated in death.

Nodules.—The test is of considerable prognostic value when subcutaneous nodules are present. There is generally an appreciable lag in the time these appear and disappear in relation to the other active rheumatic manifestations. It is therefore somewhat difficult to decide what stage the disease has reached in a particular case. Here the S.R. may be a valuable guide. Many such cases have been followed and it has invariably been found that the first indication that nodules are about to vanish is a gradual return of a high S.R. to normal (see fig. 5). Conversely a persistently raised S.R. is a clear indication that the end of the active phase has not been reached and that the nodules will remain present for an indefinite period. Many cases will continue in this manner for many months, the number of nodules varying from time to time, and the prognosis is left in doubt. Such patients are in a precarious position; many of them ultimately get well but they may suddenly become worse, and, overwhelmed by the increasing number rheumatic lesions, finally succumb (see fig. 6).

Conclusions.

1. The close relationship between rheumatic activity and the sedimentation rate has been confirmed.

2. Acute tonsillitis and influenza may both cause more than a temporary rise in the sedimentation rate. This must be remembered when making use of the test as possible evidence of active rheumatism. Chronic tonsillar infection on the other hand does not as a rule have any appreciable effect on the sedimentation rate.

3. The influence of anaemia on the sedimentation rate has been examined and a method of assessing the true value of the test in the presence of anaemia is suggested.

4. In acute chorea there is only a small, transient rise of the sedimentation rate. This may even be absent. No indication is given by the sedimentation rate of the possibility of subsequent cardiac involvement.

5. In congestive cardiac failure the sedimentation rate frequently falls to normal even in the presence of active disease. This is a bad prognostic sign.

6. The test is of value in detecting subacute rheumatism and ' miniature rheumatic fever ' following tonsillitis.

7. When nodules are present the test has a prognostic significance. Fall of the sedimentation rate heralds their disappearance.

We wish to thank Dr. A. Gordon Signy for some of the S.R. tests which he carried out in the later stages of these investigations. We are extremely grateful to the Matron and Nursing Staff of the Children's Heart Hospital, West Wickham, for their invaluable assistance throughout this work. Our

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A NOTE ON THE SERUM PROTEINS IN NORMAL INFANTS AND CHILDREN*

BY

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As a result of the work of Starling[1] the important part played by the serum proteins in the pathogenesis of oedema has secured recognition. More recently it has been demonstrated that decrease in serum protein is responsible for a reduction in the calcium content of the blood; the reason for this is that a portion of the calcium exists in combination with protein.

In the literature numerous figures are available for the serum protein content of the blood in normal adults but not for children. With regard to values given for normal children, in most instances, the total protein level, as estimated by the refractometer, is all that is available. The object of this communication is to report the results obtained in twenty-four apparently normal children between two and eleven years and in twenty-two infants and young children under two years by the micro-Kjeldhal method of Howe[2] as modified by Hawk and Bergheim[3].

Methods available.

Before recording the results a brief discussion on the relative merits of the four principal methods of measurement of the serum proteins may be made.

1. **The gravimetric method.** While, according to Peters and van Slyke[4], this is the most accurate procedure, it involves the use of a large quantity of serum or plasma and for that reason it is unsuitable for investigating the blood of children.

2. **The micro-Kjeldhal method.** By combustion with acid the protein of the serum or plasma is converted into ammonium sulphate and the amount of nitrogen present is estimated by nesslerization or distillation: albumin and globulin are determined separately by Howe's technique. The procedure is accurate and smaller amounts of blood can be used than in the gravimetric method.

3. **The colorimetric method of Wu[5].** This test is really an estimation of the tyrosine which forms part of the protein molecule. It has been shown by Tachmann and Sobotka[6] that, while in normal cases results comparable with the Kjeldhal method are obtained, in nephrosis and nephritis the

* The work was done during the tenure of a Carnegie Research Scholarship.

percentage of serum albumin estimated by this method is too high because the relative percentage of tyrosine in serum albumin and globulin is altered in these conditions.

4. Refractometry. While this procedure for estimating total proteins is much the simplest, there is a general consensus of opinion that the results are too high owing to the presence in the serum of substances other than protein causing refraction of the light rays. Linder[7] and his co-workers found the total protein of the serum to be 1·59 gm. per cent. higher than by the Kjeldhal method in normal subjects. This discrepancy is in the main due to the presence of fat. Kumpf[8], using Robertson's[9] refractometric technique, found in normal subjects fair correlation for albumin, globulin and total protein with the Kjeldhal method, but in the lipaemic sera of nephrotic patients total protein and globulin by the refractometer were much too high.

From these remarks it may be concluded that the method of choice is the micro-Kjeldhal.

The serum proteins in older children.

The ages of cases investigated were between two-and-a-half and eleven years. The series consisted of patients convalescent from rheumatism or suffering from enuresis or epilepsy. They were all afebrile and well nourished at the time of the investigation. Table 1 shows the results obtained for the total protein and the albumin and globulin of the serum. Oncotic pressure was calculated from the formula of Govaerts[10].

Total protein ranged from 6·83 to 8·24, albumin from 4·45 to 5·94 and globulin from 1·52 to 2·94 gm. per cent. The average figures were total protein 7·42, albumin 5·15 and globulin 2·27 gm. per cent. Calculated serum oncotic pressure ranged from 27·8 to 35·5 mm. Hg. These results are comparable with those published in a recent article by Peters and Eisenman[11], who made one hundred and nine estimations of total serum protein by a modification of Howe's method in fifty-two adults. They found that it lay between 6·3 and 7·7 gm. per cent. in 90 per cent. of instances. Fifty estimations of serum albumin in thirty-four subjects lay between 4·1 and 6·1 gm. per cent. but in only one case was the level above 5·5 gm. per cent. Serum globulin ranged from 0·9 to 3 gm. per cent. In only one instance did it fall below 1·4 gm. per cent. They conclude that the normal limits of variation are:—serum total protein 6·0–8·0 gm. per cent., serum albumin 4·0–5·5 gm. per cent. and serum globulin 1·4–3·0 gm. per cent.

The results of other workers who have employed Howe's method are given in table 2 together with those obtained in the present series. For purposes of comparison figures obtained by Dr. Jessie W. Ogilvie (personal communication) may be quoted. In forty-five convalescent rheumatic patients total serum protein estimated by the refractometer averaged 8·34 gm. per cent. or 0·92 gm. per cent. more than the figure obtained by the micro-Kjeldhal method in the present series.

Earlier reports have indicated that globulin is slightly higher in females than in males. In the large series of Peters and Eisenman no difference was observed, a finding in keeping with the results obtained in this work.

TABLE 1.

THE SERUM PROTEINS BETWEEN THE AGES OF TWO-AND-A-HALF AND ELEVEN YEARS IN NORMAL SUBJECTS.

SEX	AGE IN YEARS	TOTAL PROTEIN : GM. PER CENT.	ALBUMIN : GM. PER CENT.	GLOBULIN : GM. PER CENT.	CALCULATED ONCOTIC PRESSURE MM. HG.
F	4	6·84	5·32	1·52	31·4
F	2½	6·87	4·49	2·38	28·0
M	5	7·75	4·81	2·94	30·6
M	5	6·84	4·74	2·10	28·9
M	5	8·01	5·22	2·79	32·6
M	5	8·24	5·43	2·81	33·9
F	5	7·25	4·97	2·28	30·5
M	7	7·38	5·10	2·28	31·2
M	7	7·54	5·18	2·36	31·8
M	8	7·22	4·72	2·50	29·4
F	8	6·84	4·45	2·39	27·8
F	9	7·58	5·94	1·64	34·9
F	9	7·43	4·70	2·73	29·6
M	10	7·10	4·72	2·38	28·4
F	10	7·64	5·28	2·36	32·3
F	11	7·78	5·27	2·51	32·9
F	11	7·27	5·52	1·75	32·8
F	11	7·34	5·12	2·22	31·2
F	11	6·83	4·99	1·84	30·0
M	10	8·02	5·92	2·10	35·5
M	8	7·78	5·62	2·16	34·0
F	9	8·04	5·25	2·79	32·8
M	8	7·03	5·42	1·61	32·5
M	10	7·62	5·59	2·03	33·6
	Average	7·42	5·15	2·27	31·5

TABLE 2.

THE SERUM PROTEINS OF NORMAL ADULTS AND CHILDREN.

AUTHOR	SERUM OR PLASMA	NO. OF CASES	AGE	SEX	TOTAL PROTEIN GM. PER CENT.	ALBUMIN GM. PER CENT.	GLOBULIN GM. PER CENT.	CALCULATED ONCOTIC PRESSURE MM. HG.
PRESENT	S	12	CHILDREN	M	7·54	5·20	2·34	31·9
SERIES	S	12	,,	F	7·32	5·11	2·21	31·2
MCLURE ET ALII[12]	P	3	,,		7·01	4·90	2·10	30·3
SALVESEN[13]	P	16	ADULTS	M	7·00	4·44	2·58	28·0
		16	,,	F	7·02	4·35	2·68	27·7
LINDER ET ALII[7]	P	8	,,		6·73	4·11	2·61	26·2
BRUCKMAN ET ALII[14]	S	13	,,	M	6·93	5·06	1·89	30·5
		8	,,	F	7·61	4·98	2·62	31·0
KUMPF[8]	S	8	,,		7·17	4·82	2·34	29·8
MOORE AND VAN SLYKE[15]	P	9	,,		7·10	4·30	2·80	27·7
WIENER AND WIENER[23]	S	20	,,		6·40	4·60	1·70	27·7

The serum proteins under two years of age.

Several authors, using the refractometer, have reported that the serum proteins in the first months of life are lower than the adult level. Mello-Leitao[16] and Bakwin and Rivkin[17] found that the adult level for serum total protein was not attained until eighteen months. Kylin[18] stated that under two years, serum total protein ranged from 4·6 to 6·5 gm. per cent. as compared with 6·4 to 8·6 gm. per cent. in subjects over two years. He also measured serum oncotic pressure and found that it ranged from 17·0 to 26·0 mm. Hg. under two years compared to 29·0 to 37·0 mm. Hg. over that age. Levy[19] estimating total protein in twenty-nine infants, obtained results comparable with those of Kylin. Darrow and Cary[20] lend support to the results of these previous investigators with the following figures.

Age.	No.	Total protein gm. per cent.	Albumin gm. per cent.	Globulin gm. per cent.	Calculated oncotic pressure mm. Hg.
'Premature'	26	4·94	3·58	1·18	20·4
Normal newborn ...	20	5·52	3·73	1·78	23·0
5–8 months	14	6·29	4·28	2·01	26·3

The last-mentioned workers and Levy used the Kjeldhal method.

Ray and Phatak[21] on the other hand employing Greenberg's[22] modification of Howe's method found in twenty new-born infants the following averages:—Total protein 7·0 gm. per cent., albumin 5·1 gm. per cent. and globulin 1·9 gm. per cent. Govaert's formula applied to these figures gives a calculated oncotic pressure of 30·7 mm. Hg.

In this work the serum proteins have been estimated in twenty-two apparently normal infants whose ages ranged from three to twenty-three months. The majority of the cases suffered from rickets or some disease of the nervous system. None was acutely ill or had fever. Table 3 shows the results. Serum total protein ranged from 6·04 to 8·0 gm. per cent., albumin from 4·12 to 5·91 gm. per cent. and globulin from 1·13 to 2·82 gm. per cent. Calculated oncotic pressure ranged from 26·5 to 34·4 mm. Hg. The average figures were total protein 7·08, albumin 4·95 and globulin 2·13 gm. per cent., and the average calculated oncotic pressure was 30·2 mm. Hg.

Comparison of the figures for infants over three months and for older children shows little difference either in range or in average. If the infants are grouped in age periods (table 4) a slight rise is seen in serum albumin and a slight decrease in serum globulin with advancing age. The slight rise in oncotic pressure which also occurs reflects the increase in albumin.

TABLE 3.

NORMAL SERUM PROTEINS UNDER TWO YEARS OF AGE.

AGE	TOTAL PROTEIN : GM. PER CENT.	ALBUMIN : GM. PER CENT.	GLOBULIN : GM. PER CENT.	CALCULATED ONCOTIC PRESSURE MM. HG.
15 WEEKS	6·87	4·49	2·38	27·8
16 ,, ...	7·19	5·10	2·09	30·9
17 ,, ...	7·22	4·96	2·26	30·4
19 ,, ...	7·10	4·48	2·62	28·3
27 ,, ...	6·56	5·43	1·13	31·5
9 MONTHS	7·63	5·38	2·25	32·7
9 ,, ...	6·94	4·12	2·82	26·7
9 ,, ...	7·33	4·77	2·56	29·8
10 ,, ...	6·79	4·92	1·87	29·7
11 ,, ...	7·72	4·95	2·77	31·1
11 ,, ...	6·82	4·14	2·68	26·5
1 YEAR	6·04	4·83	1·21	28·5
1 ,, ...	6·41	4·92	1·49	29·1
13 MONTHS	6·31	5·05	1·26	29·5
14 ,, ...	7·69	5·21	2·48	32·1
16 ,, ...	7·64	4·95	2·69	31·0
17 ,, ...	7·91	5·39	2·52	33·2
17 ,, ...	6·38	5·04	1·34	29·6
18 ,, ...	8·00	5·22	2·78	32·6
18 ,, ...	6·55	4·84	1·71	29·0
20 ,, ...	7·33	4·82	2·51	30·0
23 ,, ...	7·31	5·91	1·40	34·4
AVERAGE ...	7·08	4·95	2·13	30·2

TABLE 4.

THE SERUM PROTEINS IN INFANTS ACCORDING TO AGE.

AGE	NO. OF CASES	TOTAL PROTEIN GM. PER CENT.	ALBUMIN GM. PER CENT.	GLOBULIN GM. PER CENT.	CALCULATED ONCOTIC PRESSURE MM. HG.
3–6 MONTHS	4	7·09	4·75	2·34	29·4
6–12 MONTHS	7	7·11	4·81	2·30	29·8
12–18 MONTHS	6	7·00	5·06	1·94	30·5
18–23 MONTHS	5	7·11	5·16	1·95	31·1

Summary.

Since few analyses of serum proteins by the micro-Kjeldhal method in normal infants and children have been published, the results of estimations in twenty-four older children and twenty-two infants are reported. No essential difference from the values obtained in adults was found in children varying in age from three months to eleven years.

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FOUR CASES OF FAMILIAL ACHOLURIC JAUNDICE :

The effect of splenectomy on red cell morphology

BY

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The lowered resistance to hypotonic saline of the red cells in acholuric jaundice has for long been known, but it is only since the advent of the Price-Jones method of accurately measuring red cell diameters, and the introduction of the cell volume index that the unique shape of the red cells has been recognized. Of late the work of Vaughan[1] has added to the knowledge of the concentration of haemoglobin within the corpuscle and more recently, while this work was in progress, Hawksley and Bailey[2] have published a paper showing the effect of splenectomy on the red cell diameter. The following series of cases largely confirms the results of these observers.

Case records.

The four cases comprise a family of two boys and two girls. The disease was transmitted to them through their father who has been proved to be a typical example of the malady. Some of his brothers and sisters and their children are also affected. Probably the paternal grandfather of the cases under discussion also suffered from this disease as he was noted for his sallow complexion. Details of the family history, and a report of a haemolytic crisis occurring in each of the cases described in this article have been published by Dr. Angus Scott[3].

All four cases were admitted to the Royal Hospital for Sick Children, Glasgow, where splenectomy was performed by Mr. Alex. MacLennan. Below is a summary of each case history. The details of differential leucocyte counts are omitted to conserve space.

Case 1. A girl aged twelve years was admitted 13.9.34; she was slightly undersized and thin. Considerable pallor and slight jaundice of skin were present and sclerotic icterus was marked. The spleen was enlarged, the lower pole being palpable two-and-a-half finger-breadths below the costal margin. The liver was not palpable. The urine contained urobilin in large amounts.

BLOOD EXAMINATION (13.9.34):—Haemoglobin (Haldane) 75 per cent.; red cells, 3,190,000 per c.mm.; colour index, 1·19; leucocytes, 6,600 per c.mm.; reticulocytes, 13·2 per cent.;

platelets, 127,600 per c.mm. Van den Bergh reaction, indirect positive ($9\frac{1}{2}$ units). The fragility of red cells was increased (haemolysis present in 0·62 per cent. saline which was the highest percentage used). A Price-Jones curve showed a marked shift to the left, M.C.D., 6·57μ, microcytosis, 16·8 per cent. The differential leucocyte count was normal. A very occasional normoblast was seen.

Splenectomy performed 17.9.34. The spleen weighed 340 gm. Microscopically the picture was typical of acholuric jaundice. There was increase of the fibrous tissue of the capsule and trabeculae. The pulp was hyperplastic, the pulp spaces being engorged with blood and the sinusoids empty and flattened. The Malpighian bodies were scattered and compressed, and in most there was central and peripheral fibrosis. In this case there was almost complete absence of free iron in the spleen.

The jaundice disappeared rapidly. A blood count one week after operation (25.9.34) showed:—Haemoglobin, 85 per cent.; red cells, 3,920,000 per c.mm.; colour index, 1·08; leucocytes, 4,800 per c.mm.; reticulocytes, 2·2 per cent.; platelets, 768,000 per c.mm. M.C.D. of red corpuscles, 6·95μ, microcytosis, 7 per cent.

The patient made steady progress, and on 22.10.34, five weeks after splenectomy, the blood count was:—Haemoglobin, 96 per cent.; red cells, 4,920,000 per c.mm.; colour index, 0·98; reticulocytes, less than 1 per cent.; platelets, 270,000 per c.mm. The fragility of red cells after operation was slightly decreased, beginning at 0·58 per cent. NaCl; M.C.D. of corpuscles, 6·71μ; microcytosis, 6 per cent. The van den Bergh reaction 0·5 units, indirect positive.

Case 2. A girl aged ten years was admitted 13.9.34. She was a pale and thin child, with a very sallow complexion and sclerotic icterus. The spleen was palpable, two-and-a-half finger breadths below the costal margin. The liver was not palpable. The urine contained urobilin in large quantities.

A blood examination on 13.9.34 showed:—Haemoglobin, 64 per cent.; red cells, 2,980,000 per c.mm.; colour index, 1·08; leucocytes, 11,000 per c.mm.; reticulocytes, 12·8 per cent.; platelets, 151,980 per c.mm. The van den Bergh reaction: indirect positive ($9\frac{1}{2}$ units). The fragility was increased as in case 1. A Price-Jones showed a shift to the left, M.C.D., 6·417μ, microcytosis 24·8 per cent. The differential leucocyte count showed no special features. No nucleated red cells were present.

Splenectomy was performed on 17.9.34. The spleen weighed 300 gm. The microscopical appearance was the same as in case 1. A slight deposit of free iron was detected in the pulp cells, at the periphery of some of the Malpighian corpuscles.

The jaundice disappeared rapidly. A blood count one week after operation showed:—Haemoglobin, 80 per cent.; red cells, 4,470,000 per c.mm.; colour index, 0·90; leucocytes, 9,000 per c.mm.; reticulocytes, 3·2 per cent.; platelets, 759,000 per c.mm.; M.C.D. of red cells, 6·84μ, microcytosis, 9·4 per cent. No urobilinuria. A blood count (22.10.34), five weeks after operation showed:—Haemoglobin, 82 per cent.; red cells, 4,850,000 per c.mm.; colour index, 0·82; leucocytes, 10,800 per c.mm.; reticulocytes less than 1 per cent.; platelets, 213,000 per c.mm. The fragility of red cells was slightly decreased, lysis beginning at 0·58 per cent. NaCl. M.C.D. of

red corpuscles, 6·33μ, microcytosis, 27·2 per cent. The van den Bergh reaction was negative.

Case 3. A boy aged eight years was admitted 21.9.34. He was moderately well nourished, but pale and with definite icterus. The spleen was palpable, its lower pole two finger-breadths below costal margin. The liver was not palpable. Urobilinuria was present.

Blood count (22.9.34) showed:—Haemoglobin, 66 per cent.; red cells, 3,090,000 per c.mm.; colour index, 1·08; leucocytes, 8,200 per c.mm.; reticulocytes, 16·2 per cent.; platelets, 131,000 per c.mm. The fragility was increased to the same degree as in case 1. The van den Bergh reaction, indirect positive ($4\frac{1}{2}$ units). A Price-Jones curve showed shift to the left, M.C.D. 6·34μ, microcytosis 27·2 per cent.

A transfusion was given (22.9.34) of 350 c.c. of whole blood and splenectomy was performed on 25.9.34. The spleen weighed 280 gm. In this case splenic fibrosis was more marked than in either of the previous cases. There was a diffuse deposit of free iron in the pulp cells, especially marked in those cells surrounding the Malpighian bodies. There was a rapid clearance of jaundice. A blood count one week after operation showed:—Haemoglobin, 74 per cent.; red cells, 4,100,000 per c.mm.; colour index, 0·88; leucocytes, 8,000 per c.mm.; reticulocytes, 1·5 per cent.; platelets, 598,000 per c.mm.; M.C.D. of red cells, 6·41μ, microcytosis, 24·4 per cent. No urobilinuria was present. The child made an uninterrupted recovery. A blood count on 30.10.34, five weeks after operation showed:—Haemoglobin, 86 per cent.; red cells, 4,890,000 per c.mm.; colour index, 0·88; leucocytes, 8,200 per c.mm.; reticulocytes, less than 1 per cent.; platelets, 502,000 per c.mm. The fragility was slightly decreased, lysis beginning at 0·60 per cent. NaCl. M.C.D. of red cells, 6·44μ, microcytosis, 16·8 per cent. The van den Bergh reaction was negative.

Case 4. A boy aged six years was admitted 21.9.34. He was thin and weakly in appearance. Considerable pallor was present with a definite icteric tinge of skin and sclerotics. The spleen was palpable, its lower pole two finger-breadths below costal margin. The liver was not palpable. Urobilinuria was present.

A blood count (22.9.34) showed:—Haemoglobin 48 per cent.; red cells, 2,810,000 per c.mm.; colour index, 0·86; leucocytes, 7,700 per c.mm.; reticulocytes, 16·4 per cent.; platelets, 155,000 per c.mm. The fragility was increased as in case 1. The van den Bergh reaction was indirectly positive ($4\frac{1}{2}$ units). A shift to the left was present in the Price-Jones curve, M.C.D., 6·39μ, and microcytosis, 22 per cent. A differential leucocyte count showed increase of neutrophiles (77·5 per cent.) and absence of eosinophiles. Normoblasts amounted to 77 per c.mm. Clinically there was no evidence of acute infection. The patient was transfused 23.9.34, receiving 450 c.c. of whole blood. Splenectomy was performed on 25.9.34. The spleen weighed 240 gm. Fibrosis and destruction of the Malpighian bodies were most obvious in this case, as also was the deposit of free iron, which as well as being present in the pulp cells was also present in the reticulum. The distribution of the iron was chiefly round the Malpighian bodies.

Again there was rapid disappearance of jaundice. A blood count one week after operation showed:—Haemoglobin, 68 per cent.; red cells, 4,450,000 per c.mm.; colour index, 0·8; leucocytes, 8,700 per c.mm.; reticulocytes, less than 1 per cent.; platelets, 842,000 per c.mm. M.C.D. of red cells, 6·65μ; microcytosis, 10·2 per cent. There was no urobilinuria. A blood count, four weeks after operation showed:—Haemoglobin, 80 per cent.; red cells, 4,780,000 per c.mm.; colour index, 0·84; leucocytes, 6,000 per c.mm.; reticulocytes, less than 1 per cent.; platelets, 809,000 per c.mm. (One week later the platelets were reduced to 576,000 per c.mm.)

The fragility of red cells was slightly reduced beginning at 0·60 per cent. NaCl. M.C.D. of red cells, 6·38μ; microcytosis, 18·0 per cent. The van den Bergh reaction was negative.

Discussion.

It will be seen from the above summaries that each of the children was suffering from a considerable anaemia showing all the typical features of acholuric jaundice, namely, normal or slightly raised colour index, increased fragility of the red cells, reticulocytosis, excessive bilirubinaemia and urobilinuria, and in addition the history of a familial and hereditary transmission. In each case the expected and now well-recognized group of changes resulting from splenectomy in acholuric jaundice was found. There was immediate cessation of excessive blood destruction, and consequent diminution of bone marrow activity, resulting in a rise of the red cell count and percentage of haemoglobin to normal or almost normal levels, and a fall of the number of reticulocytes. At the same time bilirubinaemia and urobilinuria were reduced to within healthy limits with subsequent disappearance of jaundice. As in all cases in which the spleen is removed a remarkable increase in the platelet count to 700,000 or 800,000 per c.mm., occurred and was thereafter followed by a gradual return to normal numbers. Little alteration in fragility was noted, although cases have been described where the fragility became normal or was even increased after splenectomy. In the present cases there was slight lessening of fagility.

In recent years interesting observations have been made on the peculiarity of the red corpuscles in acholuric jaundice. Although the diameter of the corpuscle is reduced, there is little, if any, change in volume, the inference being that the cell has assumed a globular shape.

Recently Vaughan and Goddard[1] have shown that the concentration of haemoglobin in the red corpuscle in acholuric jaundice is higher than in health, and in various diseases including different types of anaemia. In our cases similar findings were obtained. The technique used was similar to that described by Vaughan and Goddard, except that blood was spun in graduated centrifugal tubes instead of in the haematocrit. The calculations of the various factors were done by the formulae given by these workers.

Briefly, mean corpuscular volume (M.C.V.) is the average volume of the red corpuscle and is expressed in cubic μ. Mean corpuscular haemoglobin (M.C.H.) is the average amount of haemoglobin by weight in the corpuscle

and is given in micro-micrograms ($\gamma\gamma$). Mean corpuscular haemoglobin concentration (M.C.H.C.) gives as a percentage the amount of haemoglobin per unit volume of red cell.

The data from the present cases are shown in table I where for comparison the average figures for a group of normal children are given.

TABLE 1.

COMPARISON OF BLOOD FINDINGS IN NORMAL CHILDREN AND IN MICROCYTIC HYPOCHROMIC ANAEMIA WITH THE FINDINGS IN ACHOLURIC JAUNDICE.

	RED CELLS: MILLIONS PER C.MM.	HAEMOGLOBIN: GM. PER CENT.	VOL. OF PACKED RED CELLS PER CENT.	M.C.V. c.μ.	M.C.H. $\gamma\gamma$.	M.C.H.C. PER CENT.	M.C.D. μ.
AVERAGE OF 5 NORMAL CHILDREN	5·17	13·02	40·60	78·54	25·17	32·06	
AVERAGE OF 4 CASES OF ACHOLURIC JAUNDICE	3·02	8·52	23·95	79·08	28·2	35·46	6·41
ONE CASE OF MICROCYTIC HYPOCHROMIC ANAEMIA	3·76	4·83	21·67	57·63	12·84	22·24	

M.C.V. = Mean corpuscular volume.
M.C.H. = Mean corpuscular haemoglobin.
M.C.H.C. = Mean corpuscular haemoglobin concentration.
M.C.D. = Mean corpuscular diameter.

There is a low mean corpuscular red cell diameter with a normal cell volume, a slightly increased content of haemoglobin, and increased concentration of haemoglobin. Actually in cases 1 and 2, the M.C.V. (84·6 and 85·2 c.μ respectively) was just above the upper limits of the normal series (82·13 c.μ). In case 3, M.C.V. fell within normal limits but in case 4, M.C.V. (70·21 c.μ) was slightly below the lower limits of normal (74·21 c.μ). The haemoglobin content varied directly with the size of the cell, being rather higher in cases 1 and 2 (32·2$\gamma\gamma$ and 29·5$\gamma\gamma$) in which there was definite enlargement of the cells and only very slightly increased in case 3 and slightly below normal in case 4 (23·56$\gamma\gamma$). This is of course what would be expected, the larger cells being able to hold more haemoglobin. To show the small extent of the variations of cell volume and haemoglobin from the normal, the figures from a case of microcytic hypochromic anaemia in a child of three-and-a-half years are added. In all four examples of acholuric jaundice, however, the mean corpuscular haemoglobin concentration was higher than in the normal series, i.e. the amount of haemoglobin per unit volume of red cell

was high. This is apparently a peculiarity of the corpuscle in this disease, and as suggested by Vaughan and Goddard may be a corollary of the unique shape of the corpuscle.

The effect of splenectomy on the size and shape of the red cell in acholuric jaundice is variously stated by different authors, some asserting that normal diameter was attained, and others that no change occurred. Recently, Hawksley and Bailey[2] observed the influence of splenectomy on the corpuscle by making a series of Price-Jones curves after operation. In all their cases the mean diameter increased within the first few days (one reaching almost normal figures) but in most cases, this change was transient

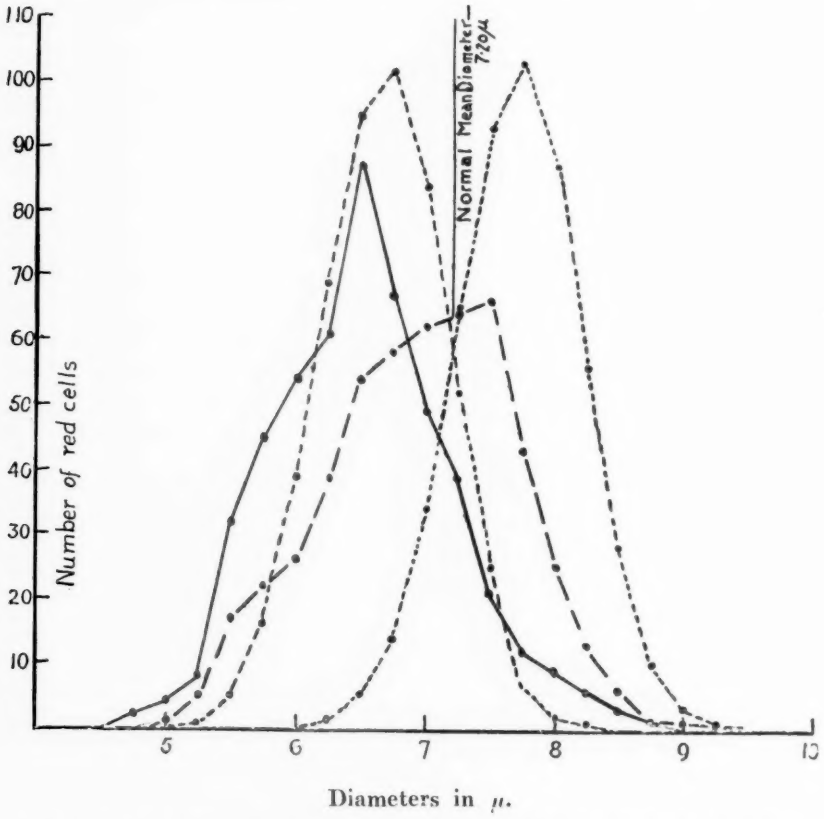

FIG. I.—Price-Jones curves in a case of familial acholuric jaundice. Mean diameter before splenectomy (continuous line) 6·57μ; mean diameter seven days after splenectomy (broken line) 6·95μ.

and a partial return to the pre-operative condition occurred. Coincident with the increase in mean diameter was a flattening of the Price-Jones curve. In the four cases discussed in this paper, Price-Jones curves were constructed before, one week after, and a month or six weeks after splenectomy. In all cases there was definite lowering of the peak in the first post-operative curves. In cases 1 and 2 a marked shift to the right occurred, the mean diameters being within normal limits although a slight microcytosis persisted in each case. An example is given in fig. 1 where, in order to make the

diagram less complicated, the final Price-Jones curve is omitted. In the remaining two cases the increase in mean diameter was of less extent. Probably the maximum increase occurred earlier than one week after operation. In all four cases, the curves constructed four to six weeks after operation had assumed a high peak, and in three cases the mean diameter had returned to almost the pre-operative figures. In the remaining case (case 1) the mean diameter (6·71μ) remained above Price-Jones' lowest normal limit (6·686μ), microcytosis being only 6 per cent. It will be interesting to note later whether the last case finally reverts or permanently maintains practically normal figures. A Price-Jones curve made by the writer on one case of acholuric jaundice, two years after splenectomy, had a mean diameter of 6·3μ, and is quite indistinguishable from the curves of the mother and other children, all of whom are affected by the disease, and who have not, so far, undergone splenectomy.

It would appear, as Hawksley and Bailey[2] suggest, that the spleen causes a further distortion of the already abnormal cell. They also suggest that possibly the remainder of the reticulo-endothelial system assumes some of the functions of the removed spleen, although if this were the case it is difficult to understand why excessive destruction of red cells should cease. It is an old argument, whether a faulty bone marrow, producing abnormally fragile red cells which are easy prey for a normally functioning spleen, or an anomalous action of the spleen on the erythrocytes is the primary factor in acholuric jaundice. Certainly the persistence of undue fragility to hypotonic saline after splenectomy in the great majority of cases seems to point conclusively to the primary implication of the bone marrow, but the effect (above described) of removal of the spleen on the size of the red cells would suggest that there are two factors concerned. Even in the early days of life increased fragility and diminished diameter of the red cells are present, so that no evidence of priority of one over the other is available.

The suggestion that the spleen exerts an influence on the red cell diameter is strengthened by the fact that in icterus gravis neonatorum, a haemolytic anaemia in which the spleen is enlarged, there is a definite diminution in the red cell diameter[1]. Further evidence should be obtained by measuring the red cell diameters in cases where the spleen has to be removed and the cell diameter is known to be normal (cases such as thrombocytopenic purpura and splenic rupture) before discussing the phenomenon with particular relation to the haemolytic anaemias with reduced cell diameter.

Summary and conclusions.

The clinical investigation of four cases of familial acholuric jaundice before and after splenectomy is reported. By measurement of the red cell diameter and volume, the globular shape and the unique increase of the concentration of haemoglobin of the corpuscle in this disease is demonstrated.

The suggestion that the spleen has a part in causing the reduced red cell diameter is supported, as after splenectomy an increase of diameter was found.

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SKIN REACTIONS TO PRODUCTS OF THE HAEMOLYTIC STREPTOCOCCUS

BY

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In the course of an investigation into the aetiological relationship of the haemolytic streptococcus to acute rheumatism, intradermal reactions to an extract of a strain of that organism were carried out on a series of 586 individuals, comprising rheumatic and control groups. Certain of the results as they relate to rheumatism are recorded elsewhere[3, 4], and a review of the relevant literature is to be found in those reports. In many cases the skin reaction of the same patient was tested at intervals, and in every case the Dick reaction was carried out and a throat swab cultured for haemolytic streptococci.

As many apparently anomalous results were noted, the investigation was pursued in order to throw further light on the phenomena of cutaneous allergy to the haemolytic streptococci, and the relationship of these reactions to the Dick reaction, apart from the question of the aetiology of rheumatic fever. The present report is a record of the findings from that point of view. Work of this kind, involving the production of severe and often painful reactions in human subjects, is difficult to carry out on a scale such as would provide results adequate for statistical analysis. Many experiments which showed promise could not be pursued further owing to lack of suitable cases, or the removal from hospital of the patients on whom tests were being carried out.

Methods and reagents.

The material used for eliciting the reaction was an extract of ground-up streptococci in 0·5 per cent. carbol-saline. The organisms were grown in broth culture, separated and washed three times in sterile saline and once in distilled water. They were then dried at 45° C. and pulverized in a ball mill. The resulting powder was suspended in 0·5 per cent. carbol-saline and at once centrifuged, the supernatant fluid being retained as the extract. Growth from 100 c.c. of twenty-four hour broth culture was used to produce 10 c.c. of extract which was diluted 1/100 for purposes of the test. A dose of 0·2 c.c. was injected intradermally. This test dose was selected quite arbitrarily as giving marked reactions in some individuals and not in others. Higher dilutions were used but they did not appear to afford any more definite differentiation between positive and negative reactors. Readings were made in twenty-four and forty-eight hours. The reaction reached its maximum in thirty-six hours.

The strain used was a haemolytic streptococcus (11CX.) isolated from the throat of a rheumatic patient. It was a typical strain of S. pyogenes in its cultural and biochemical reactions and was not related serologically to any of the scarlatinal types of Griffith. The Dick toxin and Dick control used throughout were the commercial products of Burroughs Wellcome Ltd., supplied diluted for use. In many cases repeated tests were made on the same patient at intervals of two to four weeks.

Results.

The skin reaction to H.S.E. in relation to age.*—Table 1 summarizes the results of the first test on each of the patients of the series. The incidence of positive reactions to H.S.E. increased up to ten to fourteen years and then remained practically constant. The figures for the Dick reaction suggest that the cases of the present series had more than the usual contact with haemolytic streptococci. Thus, the Dick-positive rates in all age groups were unusually low, never reaching 20 per cent. in any group of sufficient size to justify a percentage estimate.

TABLE 1.

AGE INCIDENCE OF POSITIVE SKIN REACTIONS TO HAEMOLYTIC STREPTOCOCCUS EXTRACT (H.S.E.) AND TO THE DICK REAGENTS.

AGE GROUP :— YEARS.	H.S.E. REACTION.			DICK REACTION.		
	TOTAL.	POSITIVE.		TOTAL.	POSITIVE.	
		NUMBER.	PERCENTAGE.		NUMBER.	PERCENTAGE.
0- 4	4	0	—	4	1	(25)
5- 9	122	64	52·5	105	16	15·2
10–14	108	92	85·2	99	16	16·2
15–19	54	43	79·6	47	3	6·4
20–29	100	85	85·0	83	15	18·1
30–39	81	65	80·3	68	8	11·8
40 AND OVER	108	71	65·0	90	8	8·9

Seasonal incidence of positive H.S.E. reactions.—Tests were carried out throughout four seasons of two consecutive years and in table 2 the results

TABLE 2.

H.S.E. REACTIONS CLASSIFIED ACCORDING TO SEASON.

MONTH OF YEAR.	TOTAL CARRIED OUT.	TOTAL POSITIVE.	PERCENTAGE POSITIVE.
JANUARY, FEBRUARY, MARCH	472	403	85·4
APRIL, MAY, JUNE	92	52	56·5
JULY, AUGUST, SEPTEMBER	111	79	71·2
OCTOBER, NOVEMBER, DECEMBER ...	352	292	84·1

* H.S.E. throughout this paper indicates Extract of Haemolytic Streptococcus 11CX, unless otherwise stated.

are given of skin reactions classified according to the three-monthly period in which they were performed. The majority were carried out during the winter months October to March, but the number (203) performed during the spring and summer was sufficient to show that a significant decline in the incidence of positive reactions occurred, viz. 64·5 per cent., as compared with 84 per cent., during the winter months. These figures refer to repeated tests on the same individuals. When only first tests on each patient are included the comparable figures fall to approximately 60 per cent. and 75 per cent. respectively. These data might suggest that nasopharyngeal and other infections prevalent during winter months influence the general reactivity of a population group to the antigens of streptococcus haemolyticus This suggestion is not supported by the results of throat-swab examinations in the present series (see table 3). It will be noted that the fourth quarter

TABLE 3.

INCIDENCE OF HAEMOLYTIC STREPTOCOCCI IN THROAT SWABS CLASSIFIED ACCORDING TO SEASON.

MONTH OF YEAR.	TOTAL.	TOTAL YIELDING STREPTOCOCCUS HAEMOLYTICUS.	PERCENTAGE YIELDING STREPTOCOCCUS HAEMOLYTICUS.
JANUARY, FEBRUARY, MARCH ...	536	192	35·8
APRIL, MAY, JUNE	129	39	22·5
JULY, AUGUST, SEPTEMBER ...	108	35	32·4
OCTOBER, NOVEMBER, DECEMBER	367	85	23·2
TOTALS	1,140	351	30·8

of the year was characterized by a high incidence of positive skin reactions associated with a relatively low incidence of haemolytic streptococci in throat swabs. The number of cases dealt with seemed sufficient to render the figures significant. In this connection it may be noted that the throat swabs were taken at the same time as the skin tests so that the two sets of figures refer to the same individuals throughout.

Correlation of throat culture and skin reaction.—The presence or absence of streptococcus haemolyticus in the throat swab at the time of the test did not appear to influence the skin reaction. In the presence of the organism 72·6 per cent. of 157 cases gave positive skin tests while in its absence the figure was 73·9 per cent. of 402 cases. The streptococci isolated were all examined for haemolysin production in 10 per cent. serum broth and classified as non-haemolytic if it was not demonstrable. The time-lag between throat infection and appearance of allergic skin-reaction may account for the results obtained, past rather than concurrent infection being the important factor. This was shown in scarlet fever by Gibson and McGibbon[2]. A more likely explanation is that streptococci vegetating on the surface of the pharyngeal mucosa without invading the tissues do not bring about reactivity to their products (see later).

Reactions to H.S.E. in relation to the Dick test.—Simultaneous Dick tests and tests with H.S.E. were carried out on 492 patients with the results shown in table 4; 70·1 per cent. of Dick-positive patients gave also a positive

TABLE 4.

CORRELATION OF THE RESULTS OF DICK REACTIONS WITH THE H.S.E. REACTION AND THE PRESENCE OF STREPTOCOCCUS HAEMOLYTICUS IN THE THROAT SWAB.

	RESULT OF DICK REACTION.		
	POSITIVE.	PSEUDO-POSITIVE.	NEGATIVE.
TOTAL	67	118	307
H.S.E. POSITIVE ...	47 = 70·1 PER CENT.	112 = 94·9 PER CENT.	195 = 63·5 PER CENT.
STREPTOCOCCUS HAEMOLYTICUS IN THROAT SWAB	20 = 29·9 ,,	35 = 29·7 ,,	88 = 28·7 ,,

reaction to H.S.E., while the comparable figure among Dick-negative individuals was 63·5 per cent. In view of the small number in the Dick-positive series these figures are not significantly different. This result is somewhat unexpected as it was thought that previous contact with streptococcus haemolyticus leading to the Dick-negative state would also sensitize the patient to the antigens of the organism. Pseudo-positive reactions were obtained in 118 cases (24 per cent.) and nearly all of these (94·9 per cent.) gave a positive H.S.E. reaction, a result which suggests that the constituents of filtrates responsible for the pseudo-reaction are related to the reacting substances in the ground-up bodies of the cocci.

The findings on comparing the results of the Dick test with those of throat-swab cultures (table 4) were of considerable interest. There is a remarkable similarity in the incidence of streptococcus haemolyticus in the throats of patients in the three groups, Dick-positive, Dick-pseudo-positive and Dick-negative. Haemolytic streptococci were isolated from 29·9, 29·7 and 28·7 per cent. of these groups respectively. This suggests that the majority of the haemolytic streptococci encountered were either present in the throat as non-invasive commensals or were non-toxigenic.

Repeated tests with H.S.E. in the same patient.—At intervals of two or four weeks repeated skin tests were carried out on 152 patients of our series. The number of tests on each ranged from two to ten. It was at once seen that the skin reactivity of the patients was not constant but varied in an irregular way. In some cases the initial test yielded a marked reaction which tended to show fluctuations at later tests. In others the reaction originally absent, gradually developed on repeated testing. Table 5 illustrates a few of these results taken almost at random from those patients whose stay in hospital was of long duration. The same preparation was used throughout and the technique and reading were uniform over the whole period of the tests.

No obvious explanation could be found for these variations. The reaction could not be correlated with the clinical condition of the patient. The majority were patients in a convalescent institution and were in fair

TABLE 5.

RESULTS OF REPEATED SKIN-TESTING WITH H.S.E. SIZE OF REACTION (MEAN DIAMETER IN MM.) RECORDED ALONG WITH PRESENCE OR ABSENCE OF STREPTOCOCCUS HAEMOLYTICUS (H.S.) IN THROAT SWAB (T.S.) AT THE TIME OF TEST.

NUMBER OF TEST.	CASE 124.		CASE 126.		CASE 118.	
	H.S.E. REACTION.	H.S. IN T.S.	H.S.E. REACTION.	H.S. IN T.S.	H.S.E. REACTION.	H.S. IN T.S.
1	45	—	34	—	52	—
2	22	+	20	—	20	—
3	41	—	53	—	33	—
4	54	—	55	—	21	+
5	31	—	54	—	44	—
6	30	—	31	—	20	—
7	56	—	42	—	20	—
8	44	—	42	—	20	—
9	31	—	0	—		
10	20	+	21	+		

health: the diminution of the reaction could not be attributed to debility. Throat swabs taken at short intervals frequently revealed the intermittent presence of streptococcus haemolyticus but its appearance could not be correlated with the subsequent reactions. Sometimes the reactions increased in intensity, but more frequently were altered or reduced following the finding of the organism. Two possible explanations may be offered: (1) That the skin reactivity of the patient undergoes spontaneous variation. (2) That the test injections themselves altered the reactivity. If the latter explanation is the true one it becomes necessary to postulate that the intradermal injection of a small quantity of antigen in some cases sensitizes the patient while in others it produces the reverse effect. Owing to the fact that no two individuals react in quite the same way it is impossible to control the effect on reactivity of the minimal doses of antigen used for eliciting the tests themselves.

A small series of patients was tested with repeated intradermal injections of another antigen, viz. normal horse-serum diluted 1/10 (table 6). It was then found that a reaction to horse serum might be clinically identical with

TABLE 6.

RESULTS OF REPEATED INTRADERMAL INJECTIONS OF NORMAL HORSE SERUM AT INTERVALS. DOSE IN EACH CASE 0·2 C.C. OF A 1 : 10 DILUTION OF SERUM. FIGURES INDICATE MEAN DIAMETER IN MM.

DAY OF TEST.	CASE 233.	CASE 232	CASE 201.	CASE 173.
1	0	0	0	0
3	18	16	0	12
5	23	0	0	15
7	75	24	—	—
9	73	24	—	—
11	0	35	—	—
13	0	—	—	—
15	—	—	21	75
17	—	—	17	53
19	—	—	35	64
21	—	—	37	67
23	—	—	12	0

the so-called allergic reactions to bacterial antigens. Appearing in twelve to twenty-four hours and developing to a maximum in thirty to thirty-six hours the lesion produced showed the swollen dark-red centre and peripheral pale margin as described in the case of reaction to H.S.E. The immediate wheal and erythema type of reaction was not observed in any of the fourteen cases so tested. The reactions reached a mean diameter of 90 mm. in the more marked cases.

This observation was confirmed in a series of experiments on guinea pigs in which daily intradermal injections of undiluted H.S.E. produced reactions which fluctuated in an irregular way.

These findings are of considerable importance in regard to skin reactions in general. For example, in the so-called sensitization of animals with subcutaneous or intradermal foci of infection it is customary as a preliminary to test all and to exclude those giving the reaction. Subsequent positive skin-tests are frequently attributed to the sensitizing procedure. It would appear that the intradermal route may be peculiarly effective in producing hypersensitivity to any antigenic substance.

Repeated Dick tests on the same patient.—In the course of these studies the Dick reaction was of secondary interest and all the available cases were also tested with H.S.E. This must be remembered as a possible cause of

the fluctuations observed. The number of tests which were carried out on the same patient rendered it necessary to use the Dick control only when the reaction to toxin was positive, i.e. of over 10 mm. mean diameter. The control solution was thus injected the day after the test proper since it seemed unlikely that the patient's reactivity would undergo any change in this short period.

The results shown in table 7 are illustrative of observations made over long periods in twenty-three cases. These all showed a marked variability in their reactions to the Dick reagents. The same patient might show an apparently true Dick-positive, a pseudo-positive or a negative reaction on repeated testing, while the paradoxical appearance of a larger reaction to the control fluid than to the test toxin was not infrequently observed. Commonly the test was negative on the first occasion and became pseudo-positive at a later date. Case 109 in table 7 illustrates this type. In other cases, exemplified by case 118, the test, while negative at the outset, later showed a difference between the toxin and control reactions which might normally be taken as indicating a positive result. Case 152 (table 7) is of

TABLE 7.

RESULTS OF REPEATED DICK REACTIONS CARRIED OUT AT FORTNIGHTLY INTERVALS. FIGURES INDICATE MEAN DIAMETERS OF THE SKIN REACTIONS IN MM.

TEST NUMBER	CASE 109		CASE 117		CASE 129	
	DICK TOXIN	DICK CONTROL	DICK TOXIN	DICK CONTROL	DICK TOXIN	DICK CONTROL
1	0	—	0	—	15	11
2	8	—	29	0	11	6
3	32	0	11	23	0	—
4	13	14	9	—	0	—
5	13	16	8	—	13	0
6	13	15	9	—	24	16
7	14	19	13	0	19	8
8	12	12	27	12	—	—
9	15	14	24	11	—	—
10	27	17				
	CASE 114		CASE 118		CASE 152	
1		—	0	—	20	0
2	20	14	14	0	19	19
3	18	13	7	—		—
4	24	19	6	—	0	—
5	11	0	8	—	0	—
6	7	—	—	—	6	—
7	0	—	0	—	12	14
8	17	10	15	8		—
9	20	11	17	0	23	6

interest as showing on consecutive tests a ' positive ' and ' pseudo-positive ' reaction. In all cases the H.S.E. reaction was noted at the time of the tests and while it showed fluctuations these did not correspond either to the reaction to Dick toxin or to Dick control (see table 8).

TABLE 8.

REPEATED DICK AND H.S.E. SKIN TESTS ON FOUR PATIENTS TO ILLUSTRATE THE FACT THAT NO PARALLELISM EXISTED IN THE RISE AND FALL OF REACTIVITY TO DICK TOXIN, DICK CONTROL AND EXTRACT OF HAEMOLYTIC STREPTOCOCCUS. FIGURES SHOWN ARE MEAN DIAMETERS IN MM.

TEST NUMBER	CASE 151.			CASE 166.			CASE 114.			CASE 80.		
	DICK TOXIN	DICK CONTROL	H.S.E.	DICK TOXIN	DICK CONTROL	H.S.E.	DICK TOXIN	DICK CONTROL	H.S.E.	DICK TOXIN	DICK CONTROL	H.S.E.
1	20	15	53	8		42	0	—	47	0	—	0
4	13	21	80	0		58	20	14	26	0	—	40
5	8	0	81	20	11	25	24	19	48	13	0	32
7	25	17	57				20	11	19	27	11	27

It is not suggested that a marked difference in size between Dick toxin and Dick control reactions indicated a true Dick-positive state. Rather the results suggested that the repeated intradermal inoculations of bacterial extracts and of the Dick reagents were altering the reactivity of the patient's skin to certain constituents in these latter reagents. As with the extract solution itself this reactivity showed an irregular rise and fall. It is of interest that the ' toxin ' and ' control ' reactions did not run parallel in these circumstances. They differed in their irregular periodicity and the result was the quite irregular appearance of ' true positive,' ' pseudo-positive ' and ' negative ' Dick reactions in the same individual.

At an early stage of the work this question was studied in a series of twenty-eight cases in which apparently true Dick-positive reactions were associated with a strong reaction to H.S.E. Neutralization experiments were carried out with commercial antitoxin. Mixtures were made up of commercial Dick toxin (diluted for use) of 90 per cent. strength, the antitoxin being present in a 1 in 10 dilution in the mixture. Control tests were made simultaneously with Dick toxin alone and serum alone in the appropriate concentrations. Of the twenty-eight cases no less than twenty-one reacted strongly to the serum alone and the tests were thus invalidated.

In the remaining seven the apparently true Dick-positive reaction was neutralized in five and not neutralized in two, while of the seven positive H.S.E. reactions two were neutralized. At the same time commercial antitoxin was shown to neutralize two out of three pseudo-positive Dick reactions. These results suggested that the Dick readings were inaccurate in persons receiving intradermal injections of extract. This subject will be referred to later when neutralization of apparently true allergic reactions is described.

The conditions of these tests were admittedly artificial but the question arises as to whether infection with the haemolytic streptococcus may not act in a way similar to intradermal inoculations of extract and, by altering the skin reactivity, produce anomalous results with the Dick reagents especially at the later age periods when allergic hypersensitivity is liable to develop.

Further questions arise: (1) Whether or not the ' Dick control ' solution (heated toxin) as at present used is an adequate control? It appears possible that the heating to which it has been subjected has altered the antigenic character of those proteins other than toxin whose presence in toxin requires to be controlled. (2) How is the pseudo-reacting substance of ' Dick toxin ' related to the extract of the haemolytic streptococcus? Apparently intradermal inoculation of extract will sensitize to a constituent of the filtrate and yet the undulations of this pseudo-reaction were not reflected by those of the H.S.E. reaction itself.

An explanation may be that the extract contains a number of antigens one of which is present in the Dick toxin filtrate but that others obscure its effects in tests made with the extract itself. The whole question of skin reactions to such bacterial preparations is obviously a complex one and no hypothesis involving conceptions of simple and clear-cut exotoxin and endotoxin will explain all the observed facts.

The effect of intramuscular injections of H.S.E. on skin reactivity to Dick toxin, Dick control and H.S.E. extract.—Twelve cases were inoculated intramuscularly with extract in order to demonstrate whether or not desensitization could be achieved. It was, of course, realized that the intravenous route would be more suitable but in presence of severe skin reactions this was considered an unjustifiable risk. Intramuscular injections were given at weekly intervals beginning with the skin-test dose, the quantity being gradually increased till in some cases final doses of 1·0 c.c. of undiluted extract were given. It was significant that no local, focal and general reactions were noted after any of the intramuscular injections even in patients who presented large and even alarming skin reactions.

The results showed that no constant desensitizing effect was produced and that the skin reactions to the various reagents fluctuated in a way

similar to that observed in the absence of intramuscular injections. Ilustrative examples are quoted in table 9.

TABLE 9.

INFLUENCE OF INTRAMUSCULAR INJECTIONS OF H.S.E. ON SKIN REACTIONS TO H.S.E., DICK TOXIN AND 'DICK CONTROL.'

DATE.	DOSE OF H.S E.	SKIN REACTIONS (MEAN DIAM. IN MM.)		
		H.S.E.	DICK TOXIN.	DICK CONTROL.
		CASE J.S.		
OCTOBER 10 ...	—	35	7	—
NOVEMBER 3 ...	—	14	19	8
NOVEMBER 4 ...	0·2 C.C. 1:100	—	—	—
NOVEMBER 11 ...	0·5 C.C. 1:100	—	—	—
NOVEMBER 17 ...	—	20	12	11
NOVEMBER 18 ...	1·0 C.C. 1:100	—	—	—
NOVEMBER 24 ...	0·2 C.C. 1:50	—	—	—
NOVEMBER 30 ...	—	37	22	9
DECEMBER 2 ...	0·5 C.C. 1:50	—	—	—
DECEMBER 14 ...	—	41	8	—
		CASE 114.		
OCTOBER 13 ...	—	47	0	—
OCTOBER 21 ...	0·2 C.C. 1:100	—	—	—
OCTOBER 28 ...	0·5 C.C. 1:100	—	—	—
NOVEMBER 3 ...	—	26	20	14
NOVEMBER 4 ...	1·0 C C. 1:100	—	—	—
NOVEMBER 11 ...	0·2 C C. 1:50	—	—	—
NOVEMBER 17 ...	—	41	18	13
NOVEMBER 18 ..	0·5 C.C. 1:50	—	—	—
NOVEMBER 25 ...	1·0 C.C. 1·50	—	—	—
DECEMBER 2 ...	—	25	24	19
DECEMBER 3 ...	0 2 C.C. 1:25	—	—	—
DECEMBER 9 ...	0·5 C.C. 1:25	—	—	—
DECEMBER 17 ...	—	33	11	0
DECEMBER 18 ...	1·0 C.C. 1:25	—	—	—
DECEMBER 23 ...	0·5 C.C. 1:10	—	—	—
DECEMBER 29 ...	—	16	0	—
DECEMBER 30 ...	1·0 C.C. 1:10	—	—	—
JANUARY 6 ...	0·2 C.C. UNDIL.	—	—	—
JANUARY 11 ...	—	23	0	—
JANUARY 13 ...	0·5 C.C. UNDIL.	—	—	—
JANUARY 23 ...	—	22	17	10

Neutralization of the H.S.E. reaction by antisera.—Scarlatinal antitoxin was the first serum to be employed and in order to make the conditions uniform the Dochez strain of streptococcus was employed for preparing the

extracts used in these tests. We are indebted to Dr. R. A. O'Brien for his kindness in supplying us with a subculture of the strain used in the preparation of toxin for the manufacture of Burroughs Wellcome commercial antitoxin which was the serum used. Extract-antitoxin mixtures were made up each containing H.S.E. in dilution 1:100, while the antitoxin dilution varied from 1 in 2 to 1 in 100. With the higher concentration of antitoxin, reactions to serum alone invalidated a number of the tests. In all of eighteen cases where the reaction to extract alone was definite there was no evidence of neutralization by antitoxin.

Further experiments were carried out with an antiserum prepared by immunizing rabbits with H.S.E. derived from the strain 11CX. The animals each received 74 c.c. of undiluted extract over a period of three months. At the end of that time the serum had a low agglutinating titre (1:64) for the homologous strain and also a low titre precipitating effect. Precipitates were observed up to dilution 1:10 of serum in presence of undiluted antigen and the titre of antigen was approximately the same with undiluted serum. Both serum and antigen were titrated to ascertain if the reaction had an optimal zone at high dilutions but with negative results.

Skin tests were carried out with mixtures containing 11CX extract diluted 1:100 along with the serum in dilution 1:5, control tests being made with the reagents separately. In seventeen patients tested neutralization was observed in ten, reactions up to 30 mm. in diameter being completely abolished by the serum. Neutralization did not depend on the severity of the reaction to H.S.E. alone as some very weak reactions were not neutralized.

Normal rabbit serum was found to have no neutralizing effect whatsoever on ten patients tested. The possibility of neutralizing a supposed allergic reaction even in only a proportion of test subjects was of such interest that a further experiment was carried out in which the extract of a strain serologically distinct from 11CX was employed in combination with the anti-11CX-extract serum. The strain used S_2, was from a case of severe scarlatina complicated by nephritis and was found to be of type 2 (Griffith) while strain 11CX did not belong to any of the Griffith types. Extract of S_2 in dilution 1:100 was injected with the 11CX extract serum diluted 1:5 into sixteen subjects. All reacted to the extract alone and neutralization failed except in one patient when a weakly positive reaction was neutralized. It appeared that the serum was more efficient in neutralizing reactions to the homologous extract than to others derived from serologically unrelated strains.

Nature of reacting substance in H.S.E.—While it has usually been assumed that the reactions to H.S.E. were due to the presence of nucleo-protein (Coburn[1], and others) the relatively weak antigenic power of the extract in rabbits suggested that this might not be the case. The active principle was found to be remarkably thermostable. The extract of 11CX, diluted 1:100 in 0·5 per cent. carbol-saline was steamed for one hour without loss of potency. Unheated and heated solutions were tested simultaneously on ten patients who reacted and in four the reactions were actually bigger in the case of the heated extract solutions. In one case an increase of more than 2 cm. in the average diameter of the lesions was observed. In the remaining six tests the reaction to extract (100° C.) was equal to that of the unheated. In the same way a tube of diluted extract (in 0·5 per cent. carbol-saline) was autoclaved at 15 lb. pressure for twenty minutes and tests were performed on ten reactors. In six the reaction to autoclaved extract was equal to the test with unheated reagents, while in the remaining four the lesions produced were smaller though the difference in diameter was never more than 1 cm. In no case was the reaction to autoclaved extract

negative and in six cases the lesion was over 30 mm. in diameter. This degree of thermostability is comparable to that of tuberculin.

Hydrolysis at 100° C. in alkaline solution ($\frac{N}{10}$ NaOH) inactivated the reacting property in two hours. The undiluted extract was mixed with an equal volume of $\frac{N}{5}$ NaOH and boiled in a flask fitted with a reflux condenser. The extract before and after hydrolysis was tested simultaneously on eight reactors. After one hour the product gave weak reactions in six patients while after two hours all tests were negative.

Precipitation by alcohol.—To 1 c.c. of diluted extract were added 10 c.c. of absolute alcohol and the mixture allowed to stand for two hours in the ice-chest. A flocculent precipitate formed which was centrifuged, washed once in absolute alcohol and resuspended in 10 c.c. of 0·8 per cent. saline in which it was readily soluble. A further dilution of 1 : 10 was then made for skin tests in parallel with the customary 1 : 100 dilution of untreated extract.

Tests were made on ten patients. In three cases the reaction to the purified preparation was somewhat smaller than the H.S.E. reaction but the difference was slight. In the remainder both lesions were of similar size. Apparently the alcohol-insoluble fraction contained the active principle.

Discussion.

The results recorded taken as a whole suggest that great caution is necessary in interpreting any intradermal reaction. The possibility of altering the reactivity of the patient by a test inoculation is suggested. The results recorded with horse serum are of interest and they would seem to be applicable to the various diagnostic skin reactions. For example, the repetition of the double intradermal tuberculin test in cattle at short intervals might act as a sensitizing stimulus. The present study suggests that repeated intradermal tests not only sensitize but on a continuation of the series appear to produce desensitization. Thus an irregular wave-like succession of sensitive periods is produced. It is unfortunately impossible to decide whether such variations are inherent in the individual irrespective of the test inoculations or are the result of those.

The result of the Dick tests were somewhat surprising. Only 13·6 per cent. gave positive readings and in the light of subsequent work it appeared likely that not all of these were true toxin reactions. From subsequent studies of fluctuations in the reaction to both the test and control reagents besides the failure to neutralize certain of these reactions by antitoxin, it would appear that some at least were simply the chance association of simultaneous reactivity to some constituent of the ' toxin ' fluid with temporary absence of reactivity to a constituent of the ' control ' fluid to which the individual might be at other times allergic. These findings have suggested an explanation of those pseudo-reactions when the control test is of greater size than the toxin reaction or even, as in some cases, when the control solution alone gives a reaction. The curves suggest that in the hypersensitive individual the principle responsible for ' pseudo-reactions ' to ' toxin ' and ' control ' may be regarded as different reagents, more or less distinct from one another in so far as skin reactivity is concerned.

The neutralization of reactions by homologous antiserum was of considerable interest as the effect appeared to be to some extent related to the serological type of the organism. Green[5] has reported that skin reactions to ' endotoxin ' of haemolytic streptococci varied with the serological type of the organism. The skin reaction characteristic of the allergy of infection is not neutralizable and there is no reason to think that any true antigenic toxin was responsible for the lesions produced. Further study of this problem is necessary to determine the mechanism of the neutralization process.

The results throw doubt on the conception of the skin reaction to extracts of haemolytic streptococcus as a true example of the allergy of infection, at least in adults. Myers, Keefer and Oppell[6] observed the same variations in skin reactivity to a nucleo-protein antigen prepared from extracts of this organism and also failed to discern any correlation between throat-swab cultures and skin reactions.

Summary.

The results of skin-tests employing the Dick reagents and haemolytic streptococcus extracts, and of simultaneous throat cultures on 586 individuals are described.

No correlation could be discerned between the incidence of the haemolytic streptococcus in the throat and the results of skin reactions to its products.

Repeated tests with ' Dick toxin ' and bacterial extract in the same patient revealed a marked variability in the skin reaction to the reagents used. This could not be related to the clinical condition of the patient nor to the presence of the haemolytic streptococcus in the throat. Analogous results were obtained following repeated intradermal inoculation of diluted normal horse serum.

Dick toxin and Dick control reactions did not run parallel in their fluctuations with the result that the patient might present what appeared to be a true Dick-negative reaction, a positive and a pseudo-reaction on successive tests.

Intramuscular injection of extract did not produce local, focal or general reactions and did not appear to influence the skin reaction.

Neutralization of the reaction to bacterial extract was produced in a proportion of cases by an antiserum prepared by immunizing an animal with extract. The reaction to an extract of a serologically unrelated strain was not neutralized by the serum.

Evidence is presented of the marked thermostability of the skin-reacting principle in extracts. Autoclaving a dilute solution at 120° C. produced little diminution of potency.

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THE MEDICAL TREATMENT OF CONGENITAL PYLORIC STENOSIS*

BY

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Even outside paediatric circles the clinical picture of congenital stenosis of the pylorus is nowadays well known, although Bloch as late as 1906 wrote that 'stenosis pylori congenita' was not recognized by paediatricians until several years after Hirschsprung described it in 1887, and even then in 1906 it was little known to the medical profession in general. Since then the disease has been much described and discussed. That it is not an unusual malady appears from the fact that in the Children's Department of the Rigshospital alone more than 200 cases of it have been treated in the course of twenty-three years.

The various authorities agree with regard to the clinical description, but there the unanimity ends. There are highly diverse opinions as to the pathogenesis, and equal disagreement as to the treatment. As regards the pathogenesis only some of the usual points of view which have come to the fore will be touched on here, without any definite conclusions.

Pathogenesis.

Wernstedt, who has devoted much time to investigating the pathogenesis of the disease, believes that its spastic nature is indisputable but he doubts whether there can be spasm without hypertrophy of the pylorus, and therefore whether hypertrophy of the pylorus is congenital or a secondary compensatory hypertrophy. Monrad believes it to be a question of congenital hypertrophy of the pylorus with intermittent spasms and that both tend to disappear as the infant grows older. Bloch considers the cause of the disease to be a remnant from foetal life, of the foetal pyloric canal, with hypertrophy and spasm of its musculature and compensatory hypertrophy of the rest of the musculature of the stomach. When this foetal formation disappears and the pylorus is closed by a sphincter the symptoms vanish. There is nothing to indicate that the patients have any trace of the disease in later life. Povl Hertz believes that the malady is due to a spasm which is a secondary factor in a congenital, hypertrophied pylorus musculature. Heile and others think that it is possible to find pyloric spasm both with and without hypertrophy of the pylorus. Meuwissen and Sloof, on the basis of x-ray examinations, believe that one may conclude that the hypertrophy of the muscle is probably a result of the spasm. Lehmann believes it to be a question of a congenital, functional

* Translated from the Danish by Elsie-Marie Werner Kornerup, B.A.

pyloric obstruction with compensatory muscle hypertrophy and hyper-irritability of the vagus centre. Various other authors, especially French and American, believe that there are two diseases, pyloric spasm and pyloric stenosis, which certainly cannot be differentiated from one another except by demonstration of the thickened pylorus. Peiffer believes that the malady arises from vagotonus or sympathetic hypotonus with relative vagotonus.

In all cases, spontaneous recovery takes place provided the patient does not die of inanition during the course of the disease. Treatment must therefore aim at preventing this.

Principles of treatment.

There has been a great deal of discussion about the principles involved in treatment. Two main points of view are outstanding: i.e., preference for surgical measures on the one hand and, on the other, conservative medical treatment. In some places both methods are in use, depending upon the nature of the case. There seems, however, to be an increasing tendency towards preference for surgical measures.

The medical treatment at the different clinics varies to some extent. There is, however, conformity of opinion as to the fact that first of all the dehydration must be combatted with saline, given subcutaneously, intravenously and per rectum. The methods of nourishment, on the other hand, vary greatly. In some hospitals frequent feeds, every hour or every two hours, are given. In this case the quantity given is small, beginning with 10 or 20 gm. at a time. Sometimes common milk-modifications are chosen sometimes human milk or butter-milk. Concentrated porridge-like mixtures, consisting of, for example, rusks softened in evaporated milk, have been warmly recommended.

Kleinschmidt (now of Cologne) gave at the University Clinic in Hamburg human milk evaporated in vacuo until it was of the consistency of porridge (reported by Ebert). Casein milk, baby foods, such as, for example, larosan, have also been recommended. As for medicines, atropin has been used sometimes and during recent years, use of eumydrin has been occasionally reported. None of the remedies seems to have been given consistently, and widely differing judgment has been passed upon their effect. Papaverin and vasano have also been tried. Eckstein believes that the vomiting is due to hyper-irritation of the vagus centre and he therefore recommends hypnotics, such as adalin, noctal and somnifen. He has seen good results in eight cases thus treated. Washing out the stomach in order to remove its decomposing contents and thereby avoiding the complication of gastritis is still often undertaken. Nourishment has also been given through a duodenal tube.

Surgical therapy is by far more uniform. Gastro-enterostomy was long ago discarded in favour of Rammstedt's operation which consists of cutting through the pyloric musculature longitudinally, so that the mucous membrane is reached through the muscle bundles and the pylorus made to gape. This operation, with slight modification has become almost universal.

The indications for operation are variously regarded. Rammstedt and others advise operation when, after eight or ten days of medical treatment, there is no improvement in the patient's condition. All agree that the

success of the operation depends upon the child's not being too ill at the time. Bayer goes so far as to say that the condition of the child before the operation is more important for the success of the latter than the surgical technique. All authorities lay great stress upon the post-operative treatment, and the necessity of co-operating with the paediatric department is emphasized. Those who favour operation state that as a consequence the symptoms disappear quickly, in fact, often suddenly, and the duration of the disease is shortened, since the after-treatment often need only extend over a period of from two to four weeks.

Previous results.

The following statistics show the results of medical and surgical treatment respectively in various clinics.

TABLE 1.

MEDICAL TREATMENT.

YEAR.	PAEDIATRICIAN.	NO. OF CASES.	MORTALITY.
			PER CENT.
1921	ERNBERG AND HAMILTON	57	3·5
1922	IBRAHIM	52	1·9
1928	MONRAD	228	4·4
1930	WOLFF	98	2·2
1933	FAXÉN	126	3·3

TABLE 2.

SURGICAL TREATMENT.

YEAR.	PAEDIATRICIAN.	NO. OF CASES.	MORTALITY.
			PER CENT.
1926	ABT AND STRAUSS	221	3
1926	HEILE	42	2·4
1927	TISDALL, POOLE AND BROWN ...	120	13·2
1929	HABERER	35	2·2
1932	HABERER	73	5·5
1934	HABERER	102	6·9
1930	RAMMSTEDT	60	3·3
1933	NISSEN AND BOECKER	50	8

TABLE 3.

TREATMENT PARTLY MEDICAL, PARTLY SURGICAL.

YEAR.	PAEDIATRICIAN.	MEDICAL TREATMENT.		SURGICAL TREATMENT.	
		NO. OF CASES.	MORTALITY.	NO. OF CASES.	MORTALITY.
			PER CENT.		PER CENT.
1929	BAYER	40	2·5	46	26
1929	BIRK	56	18	20	0
1933	BEHRMANN ...	61	18	50	28
1933	MUNTING * ...	66	16·6	58	12
1933	WIEDHOPF ...	35	5·7	15	13·3
1933	WILLI	87	5·7	37	24·3
1934	ECKSTEIN ...	92	18·4	110	3·4

* In Munting's material, the first 20 who received operative treatment are the same as in Birk's statistics. All cases of death, therefore, occurred in the last 38 cases.

In 1930 Rammstedt had collected information about 1,842 cases from sixty different clinics. Of these, 1,345 had received medical treatment with a mortality of 16 per cent. and 497 were treated surgically with a mortality of 22·5 per cent. The statistics of the mortality for those treated medically as well as surgically are, on the average, more encouraging in those hospitals which confine themselves to one of the two methods. This may indicate that hospital discipline and consistent treatment are of importance. On the whole, the mortality rate seems to be lower in the case of medical treatment.

Present material.

In spite of the best possible technique it is scarcely possible to avoid a certain mortality as a direct result of the operation. In order to counterbalance the growing enthusiasm for operation, it is felt to be justified to publish the following material from the Children's Department of the Rigshospital, where the treatment has always been exclusively medical.† The material covers the period from 1911 to 1934. During this time 224 patients were treated. A number of slight cases which recovered rapidly following admission to the hospital and received no special treatment have, however, been deducted, and also a few in which the diagnosis was made only on the basis of gastric peristalsis and vomiting, and four cases in which death occurred, the details of which are as follows:—

† The numerical statistical work was undertaken in collaboration with G. Rasch, Ph.D.

One patient died immediately after admission; another within twenty-four hours of pyelonephritis; a third on the second day with hyperpyrexia and convulsions due to nephritis; and finally, a patient, aged one week, who had been born six weeks prematurely. In this case no diagnosis was made, but autopsy revealed pyloric stenosis. The patient's vomit had been bile-stained.)

The final material, therefore, consists of 179 cases. In order to establish the diagnosis of congenital pyloric stenosis the following signs and symptoms were required:—the presence of projectile vomiting, gastric peristalsis, emaciation and constipation. Furtherfore, in most cases (155, i.e. 87 per cent.) there was a palpable pyloric tumour. In a few cases constipation was not especially pronounced but the other symptoms were typical. In sixty-two cases there were traces of blood in the vomit and melaena. X-ray examinations were not made.

As in other collected series of these cases it was found that by far the majority of patients were boys (135 boys and 44 girls, i.e. 75 per cent. boys). Sex seems, however, to play no part, as far as the course of the disease is concerned. The present results agree with those of Faxén that there is no evidence of any seasonal distribution. Hereditary tendency was observed in five cases. In one, the father had had pyloric stenosis. In the case of three patients who were the second children in a family, the eldest children (two boys and one girl) had also had the disease. In the case of one child, the fourth in the family, two brothers had had pyloric stenosis. In one case the mother was said to be 'nervous,' in another, an habitual drunkard. No mention was found in the other case-histories of nervous disorders in the parents.

Ninety-nine, i.e. 56 per cent. of the children, had been breast fed until the appearance of symptoms. Only thirty-five, i.e. 20 per cent., had received entirely artificial feeding. This proportion has been the same throughout the years. The number of breast-fed infants is scarcely larger than for any other group of infants. There are, however, no reliable figures as to the proportion of breast-fed and bottle-fed babies among the population during the corresponding period. The type of feeding previous to the disease does not seem to influence its course.

The following complications were found: Minor catarrhal conditions, nine cases; tonsillitis, four; thrush, one; bronchitis, one; broncho-pneumonia, three; otitis media, seven; pyuria, twelve; albuminuria, three; septicaemia, one; pemphigus, one; pertussis, two; varicella, two; dyspepsia, four; inguinal hernia, thirteen; prolapse of rectum, one; pes equino-varus, one; icterus neonatorum, two; prematurity, three; simple anaemia, ten.

The material falls naturally into three groups, in which three different therapeutic measures have been systematically used.

Group I. 1911-1927. Gastric lavage and, to some extent, feeding through a duodenal tube.

Group II. 1922–1927. Atropin.

Group III. 1927–1934. Eumydrin.

(Some of the patients in groups I and II have been discussed by Hertz in 1915 and Johannesen in 1924.)

In 147 cases the diagnosis under which the patients had been sent to the hospital was congenital pyloric stenosis or suspicion of it. Other diagnoses have been: infantile atrophy, dyspepsia, enteritis, gastro-enteritis, melaena, vomiting, observation for ileus and oesophageal stricture.

It appears that in recent years the physicians consulted send the patients to the hospital at an earlier stage. Thus it is seen that within four weeks after the onset of the disease 55 per cent. of the patients were admitted in the first group, 64 per cent. in the second group and 72 per cent. in the third group. The duration of home treatment has apparently become shorter. It is rarer now for a patient to be admitted in a state of extreme atrophy, but none the less, 59 per cent. of the patients in group III weighed less than at birth.

With regard to further therapeutic details, it must be emphasized that common to all three groups is the thorough treatment of dehydrated patients with saline. Until the diuresis is satisfactory, saline is given in the form of subcutaneous injections, consisting of 100 c.c. at a time, once or twice a day. At the same time, and later alone, saline is given per rectum (75 to 100 c.c. for a couple of weeks). After a time this usually causes some rectal irritation which makes the patient evacuate the saline at once. The theoretical basis for this saline therapy has been expounded in recent years by Schnorr, Seckel and others. It has been shown that because of the severe vomiting the body becomes extremely deficient in chloride and the patient can go into a hypochloraemic coma. In view of this Seckel disapproves of gastric lavage which makes the body still more deficient in chloride.

The principles regarding nourishment have been more or less the same throughout the years. Feeds are not given any more frequently than is usual at that age, i.e. seven a day, but only small quantities are given, i.e. 60 to 75 c.c. at a time. Milk, diluted with barley-water, is given but the milk mixture is more concentrated than for healthy infants of the same age. In recent years 6 per cent. sugar has been added instead of the customary 2 per cent. Buttermilk was widely used the first few years, but since it did not appear to offer any particular advantages, it is now an exception to give it. When the patient has drunk half the contents of a bottle, a pause in the feed is made and the bottle removed for five or ten minutes. If vomiting takes place 35 c.c. more are given. Human milk is used extensively, a few of the feeds consisting of it, the rest of milk modifications. In order not to waste the human milk it is not given as long as the vomiting is severe. Nutritional enemas, as recommended for example by Ibrahim, have not been given. In view of the danger of contagion, these patients are usually kept in small wards, or, if several are admitted at one time, in one larger ward. Care is taken not to have them in the same room with patients suffering from catarrhal or other contagious diseases. Furthermore, there are no patients over one year of age on the floor of this ward.

As already mentioned, during the period from 1922 to 1927 the outstanding feature of the therapy was gastric lavage to remove the decomposing contents of the stomach and, from 1916, feeding through a duodenal tube. Five out of seventy-one patients died. In four of the cases death must be attributed entirely to emaciation resulting from the

pyloric stenosis. In the fifth case there was broncho-pneumonia simultaneously.

During the second period, at Arne Johannesen's incentive, a 1 in 1,000 solution of atropine sulphate was given by mouth, beginning with one drop (=0·05 mgm.) per dose, and increasing to, at the most, two drops, seven times a day, when seen to be well tolerated. Sometimes this treatment was kept up for two or three months until the vomiting had ceased and the patient was thriving satisfactorily. Now and then atropine poisoning was observed. In this event, no atropine was given at the next feed or possibly the dose was decreased, or the treatment stopped for a few days and then cautiously begun again. In some cases the temperature was raised to about 38° C. (100·4° F.), a fact which must be attributed to the atropine. No serious cases of atropine poisoning were observed. A few patients did not respond to the treatment. In the beginning of this period a few of the patients were still treated with gastric lavage, a method of treatment which has gradually been abandoned. The patients who received atropine stopped vomiting more quickly and thrived better than previously. Three out of forty-seven died. In all three cases the cause of death was emaciation resulting from pyloric stenosis. One case was complicated by broncho-pneumonia.

In 1927 treatment was started with eumydrin which Paul Drucker, at that time on the staff of the department, had found to be a comparatively non-poisonous, yet particularly efficacious atropine compound. Eumydrin is atropinemethylnitrate. It is said to be fifty times less poisonous than atropine, although the efficacious dose is only two or three times larger. Usener and a few others (Ebert, Herbst and Lindquist) recommended it as being worth a trial in congenital pyloric stenosis. In this department it is given in a 1 in 10,000 solution. Since such a solution does not keep, a fresh one is always given, i.e. not more than one week old. Five c.c. of this, corresponding to 0·5 mgm. per dose, are given seven times a day, half an hour before each feeding. During recent years, however, a start has been made with only 0·25 mgm. per dose, which in a number of cases has proved to be sufficient.

This treatment is kept up for weeks, i.e., until the patient has not vomited for a week or more. In some cases the vomiting begins again after the eumydrin has been discontinued. Providing this occurs eumydrin is again given until there has been no vomiting for a week or longer. It is extremely unusual to have to repeat the treatment a third time. Serious recurrences have not been observed. The skin of the patients is often seen to be a clear, flaming red and a few times there has been a rise of temperature up to about 38° C. (100·4° F.). Apparently this must be attributed to the eumydrin. In these cases no eumydrin is given at the next feeding. The attack always passes very quickly. Friedlaender has described a case of eumydrin poisoning with hyperpyrexia and death (no autopsy). Monrad reported that a brother of the patient also reacted with hyperpyrexia when given eumydrin. It may, therefore, be concluded that this was a case of idiosyncrasy.

As mentioned above, neither during eumydrin nor atropine treatment, has severe poisoning been encountered. The precautionary measure is always observed not to give these drugs as long as the patient is in an extremely dehydrated condition: not until the introduction of saline has produced satisfactory diuresis is the medicine given.

During the period of eumydrin treatment, two out of sixty-one patients died. In one case all the symptoms of pyloric stenosis had disappeared several weeks before death took place, and the patient was thriving well. He contracted a severe pyelonephritis, and death must be attributed to that alone. Autopsy revealed a medium-sized pyloric tumour and a severe bilateral pyelonephritis.

In the other case the patient did not respond to eumydrin treatment.

When admitted to the department she was seven weeks old and weighed 200 gm. less than at birth. She had pes equino-varus of both feet. The vomit contained blood and she continued bleeding for a long time following the needle-prick for the saline injection. As stated above, the eumydrin had no effect upon her and it was therefore discontinued at the end of three weeks. The patient's temperature, upon admission was 38·4° C. (101·2° F.) and next day (before she had received eumydrin) it was 39° C. (102·2° F.). It was normal during the next ten days but rose again to 38° C. (100·4° F.) and 39° C. (102·2° F.). On the last day (after the eumydrin had been abandoned) her temperature rose to 41·2° C. (106·6° F.). There is no definite explanation for this rise of temperature. There was no pyuria, but slight albuminuria. At autopsy a pyloric tumour was found as well as dilatation of the stomach and oesophagus and a fatty liver.

In this case, medical treatment did not help, but in view of the patient's debility and haemorrhagic diathesis, neither could surgical treatment have saved her.

Discussion of results.

It is common to evaluate the efficacy of a method of treating congenital pyloric stenosis in the light of its mortality rate. This way of regarding it, however, gives only a highly imperfect picture of what is achieved. As a rule, the material includes only a small number of patients and therefore one death can have considerable influence upon the figures: (cf. inter alia, Munting-Birk's statistics on patients treated surgically and Haberer's increasing mortality rate).

In our material in Group I, 5 out of 71 died, i.e. 7·1 per cent.
,, ,, ,, ,, ,, II, 3 ,, ,, 47 ,, ,, 6·4 ,, ,,
,, ,, ,, ,, ,, III, 2 ,, ,, 61 ,, ,, 3·3 ,, ,,

If the case is omitted in which death must be attributed to pyelonephritis a mortality rate of only 1·6 per cent. is obtained. The mortality rate is lowest in the case of patients treated with eumydrin, but in all three groups the figures are the same category. Only when the results of the treatment in the case of discharged patients are regarded is a clear impression obtained: it is found that eumydrin treatment is unquestionably the most successful.

It is worth noting that all of the patients who died had blood in the vomit and melaena. Also, patients who recovered respond more slowly to the treatment when they have a tendency to bleed: 62 out of 179 had this tendency. In the first period there were 31 out of 71, in the second, 15 out of 47 and in the third 16 out of 61.

The following table will give a summary of the condition of the bleeders upon admission.

TABLE 4.

Condition	Group I	Group II	Group III	Totals	Percentage
Atrophied	10	6	5	21	34
Thin and dehydrated	7	5	4	16	26
Thin	9	2	6	17	27
Not emaciated ...	5	2	1	8	13
Total	31	15	16	62	

The average length of time spent in the hospital (not including those that died) is respectively 120, 102 and 102 days.

Patients without a tendency to bleed fall into the following groups as far as condition when admitted is concerned.

TABLE 5.

Condition	Group I	Group II	Group III	Totals	Percentage
Atrophied	16	6	6	28	24
Thin, dehydrated ...	10	10	22	42	36
Thin	11	12	8	31	26
Not emaciated ...	3	4	9	16	14
Total	40	32	45	117	

The number of days these patients (non-bleeders) spent in the hospital is on the average, respectively 101, 94 and 69.

The figures show that the patients with a tendency to bleed were more seriously ill than the others, even though when admitted they were not always the most emaciated or apparently the most miserable, and although the loss of blood in itself was not considerable. It might be thought that the bleeding was due to a mechanical lesion of the mucous membrane of the stomach, brought about by the severe vomiting, but this does not account for the more severe course of the disease in the case of

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The figures show that the patients with a tendency to bleed were more seriously ill than the others, even though when admitted they were not always the most emaciated or apparently the most miserable, and although the loss of blood in itself was not considerable. It might be thought that the bleeding was due to a mechanical lesion of the mucous membrane of the stomach, brought about by the severe vomiting, but this does not account for the more severe course of the disease in the case of

these patients. Presumably, the bleeding is rather an indication of haemorrhagic diathesis which is not congenital in these children, but appears at the same time as the first violent symptoms of the disease, and is a result of the severe vomiting with its great loss of fluid and salts. The body suffers from acute inanition, which also makes its presence known through the glycosuria often found in these children at the beginning, and which must be classified as hunger-glycosuria. Frequently the inanition has not yet reached the point at which it is recognizable through considerable loss of weight. The tendency to bleeding disappears when the feeding is in order. This applies to both breast-fed and bottle-fed infants. The seriousness of the bleeding symptom does not seem to have been previously emphasized as strongly as it obviously deserves to be.

The influence which the duration of the illness prior to admission has upon the condition upon admission, is shown by the following table.

TABLE 6.

Condition when admitted	Bleeders		Non-Bleeders		Total	
	No. of patients	Length of illness in weeks	No. of patients	Length of illness in weeks	No. of patients	Length of illness in weeks
Atrophied	21	5·6	28	4·5	49	5
Thin, dehydrated ...	17	3·6	42	3·9	59	3·8
Thin	16	3·5	32	4·1	48	3·9
Not emaciated ...	8	2·6	15	2·6	23	2·6
Total	62	4·1	117	4·0	179	4·0

The condition upon admission is seen to be in a high degree dependent upon how much time elapsed previous to it. There is not any appreciable difference between bleeders and non-bleeders, in this respect.

If all of the patients are taken collectively it is seen that in all three periods, on the average, the weight at birth is good but that the patients are considerably emaciated upon admission.

TABLE 7.

	Group I. 71 Patients.	Group II. 47 Patients.	Group III. 61 Patients.
Average weight at birth	3475 gm.	3640 gm.	3460 gm.
,, ,, upon admission ...	3172 ,,	3358 ,,	3410 ,,
Percentage of Patients weighing less than at birth	58	66	59

In by far the majority of cases the first symptoms appear between the second and fifth week of life.

TABLE 8.

Symptoms began.	Group I.	Group II.	Group III.
At birth	13	3	2
1st week	8	2	5
2nd ,, ...	13	16	16
3rd ,, ...	14	11	17
4th ,, ...	2	4	6
5th ,, ...	14	8	9
6th ,, ...	4	0	3
7th ,, ...	0	1	0
8th ,, ...	0	0	1
9th & 10th week	3	2	2

TABLE 9.

Age upon admission.

	Group I.	Group II.	Group III.
Less than 3 weeks	4	1	2
,, 3 ,, ...	7	7	10
,, 4-5 ,, ...	21	13	21
,, 6-7 ,, ...	15	13	9
,, 8-11 ,, ...	15	9	16
,, 3 months	7	4	1
,, 4 ,, ...	0	0	2
,, 5 ,, ...	1	0	0
,, 6 ,, ...	1	0	0

In order to examine more closely the effect of the treatment upon the patients, the following figures have been compiled from the material.

TABLE 10.

	Group I.	Group II.	Group III.
Average time when vomiting stopped after patient was admitted*	6 weeks.	4¼ weeks.	3 weeks
Duration of the initial loss of weight	4½ weeks	2½ weeks	1 week

* Short recurrences (one or two vomits) which occurred later in the course of the disease have not been taken into consideration.

The conditions for bleeders and non-bleeders can be seen in more detail in the following table.

TABLE 11.

	Average time during which patient vomited.		Length of initial loss of weight.	
	Bleeders.	Non-bleeders.	Bleeders.	Non-bleeders.
Group I. ...	7 weeks	5·4 weeks	5·9 weeks	3·9 weeks
Group II. ...	5·9 ,,	4·0 ,,	2·7 ,,	2·4 ,,
Group III. ...	3·8 ,,	2·8 ,,	1·2 ,,	0·7 ,,

Marked progress is noticeable during the period of atropine treatment (group II). It is still more striking during that of the eumydrin treatment (group III), even as far as patients with a tendency to bleed are concerned. It is usually on the average only from one to two weeks, before the bleeders stop losing weight and less than a week for non-bleeders. In 56 per cent. of the cases the patients begin to gain weight a few days after the eumydrin treatment is begun.

Additional confirmation as to the excellence and superiority of eumydrin treatment compared to previous methods, is given by the following statistics:—

TABLE 12.

	Group I	Group II	Group III
1. Initial loss of weight	0·263 kgm.	0·230 kgm.	0·089 kgm.
2. No initial loss of weight	15 cases=21 per cent.	6 cases=13 per cent.	31 cases=50 per cent.
3. Average weight when discharged	3·995 kgm.	4·540 kgm.	4·650 kgm.
4. Average increase in weight from weight when admitted	0·950 kgm.	1·27 kgm.	1·27 kgm.
5. Average increase in weight per week	62 gm.	91 gm.	122 gm.
6. Average increase in weight per week from time when patient ceased to lose weight	117 gm.	131 gm.	147 gm
7. Average no. of days spent in the hospital (fatal cases not included)	108	96	77

Thus it is seen that the patients treated with eumydrin were in the hospital a much shorter time than those in the other two groups. This also applies to the patients who were atrophic and dehydrated upon admission and is illustrated by the following figures, which show that even these patients recovered much more rapidly.

TABLE 13.

	Group I		Group II		Group III	
	Average no. of days in hospital	No. of patients	Average no. of days in hospital	No. of patients	Average no. of days in hospital	No. of patients
Atrophied, dehydrated and emaciated (not counting the bleeders)	101	26	94	16	76	28
Thin, but not dehydrated and emaciated ...	100	14	94	15	56	17
Totals	101	40	94	31	69	45

(This difference, as far as the bleeders are concerned, is not so striking, since, as already mentioned, both in the case of atropine and eumydrin treatment the illness lasted 102 days, while in the first group it lasted 120 days.) If the figures dealing with the time spent in the hospital are examined, it is seen that it is of equal length in groups I and II, whether or not the patients were severely ill when admitted. It is only in group III that good condition upon admission served to shorten confinement to the hospital.

In the light of these results there can be no doubt as to the efficacy of eumydrin treatment. In order to secure such good results from medical treatment it is undeniably of the utmost importance that the nursing should be extremely careful and systematic. In this respect it must be recorded that the best possible support from the nurses, some of whom participated in the treatment from its very start, has been available. It devolves upon the nurses to see that feeding is correctly carried out, and that the eumydrin is given half an hour before feeding, in order that it may exercise its effect when the food enters the stomach. Furthermore, it depends, to some extent, upon the nurses whether or not a child escapes infection.

That the average duration of stay in hospital, in the case of patients receiving the eumydrin treatment, is comparatively long, (i.e. seventy-seven days), is due to the fact that it is not considered advisable to discharge patients before they have been gaining steadily in weight for a long time. They are therefore kept after the clinical symptoms have disappeared. One of the objections made to conservative treatment, especially by German paediatricians, is its long duration. This, however, can only be of

consequence where public welfare is not able to assist the parents with the hospital expenses, or where there is a lack of accommodation in the hospital. The infant itself misses nothing by staying in the hospital.

It is evident, then, that the medical treatment in the Rigshospital Children's Department has been so satisfactory that there is no reason to change to surgical treatment, and still less, to accept the statement that not to operate is unjustifiable.

Summary

From 1911 to 1922 in the Children's Department of the Rigshospital, Copenhagen, congenital pyloric stenosis was treated by gastric lavage and feeding through a duodenal tube.

From 1922 to 1927 atropine was given and since 1927, eumydrin. During these periods respectively, 71, 47, and 61 patients were treated. The following summarizes the results in these three groups of patients: the average number of days spent in the hospital were 108, 96 and 77 and the mortality 7·1 per cent., 6·4 per cent. and 1·6 per cent. The average initial loss of weight (not including the fatal cases), was 0·263 kgm., 0·230 kgm., and 0·089 kgm. Average weight upon discharge was 3,995, 4,540 and 4,605 kgm. The average increase in weight was 0·95, 1·27 and 1·27 kgm. The average increase in weight per week was 62, 91 and 122 gm.

The satisfactory results of eumydrin and its superiority to the two other methods of treatment are not emphasized so much in the light of its mortality rate, which is low in all three periods (and where the number of cases is also too small to permit the drawing of definite conclusions), but with regard to the results of the treatment as seen in the patients discharged.

Great stress is laid upon: (1) Saline administration while the patient is still in a dehydrated condition. (2) The giving of atropine and eumydrin only when the dehydration is over. (3) The giving of the drug half an hour before feeding.

The more serious prognosis for patients with a tendency to bleeding is emphasized.

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